Search Notes 6/04 dcp

WEST Search History

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DATE: Thursday, June 03, 2004

Hide?	Set Name	Query	Hit Count
		DB=USPT; PLUR=YES; OP=AND	
☐	L1	constant.clm. and region.clm. and ($variable or variabl$).clm.	2042
☐	L2	(lipoteichoic or lipo-teichoic or teichoic or teichoicacid or lta or antilta or anti-lta or polyol or ribitolphosphate or ribitol or glycerolphosphate or glycerol-phosphate).clm.	14831
☐	L3	L2 and l1	1
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND	
☐	L4	constant.ti,ab,clm. and region.ti,ab,clm. and ($variable or variabl$).ti,ab,clm.	4897
☐	L5	(lipoteichoic or lipo-teichoic or teichoic or teichoicacid or lta or antilta or anti-lta or polyol or ribitolphosphate or ribitol or glycerolphosphate or glycerol-phosphate).ti,ab,clm.	68854
☐	L6	L5 and l4	48
		DB=EPAB; PLUR=YES; OP=AND	
☐	L7	WO-9857994-A2.did.	1
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND	
☐	L8	(moab or mab or hybridoma or monoclonal or mono-clonal).clm.	11879
☐	L9	(humanized or humanization or humanizing or chimeric or chimer$)	46403
☐	L10	(staph or staphepi or epi or epidermidis or aureus or grampositive or gram-positive or staphylococcus or staphylococci)	72741
☐	L11	L10.clm.	3317
☐	L12	L11 and l8 and l9 and l10	56

END OF SEARCH HISTORY

teichoic acids (tī-kō'ik)

One of two classes (the other being the muramic acids or mucopeptides) of polymers constituting the cell walls of Gram-positive bacteria, but also found intracellularly; linear polymers of a polyol (ribitol phosphate or glycerol phosphate) carrying d-alanyl residues esterified to OH groups and glycosidically linked sugars.

Prev

wall teichoic acid, any of various teichoic acids that are attached to *N*-acetylmuramic acid residues of the peptidoglycan of gram-positive bacteria; they may serve as antigenic determinants for certain bacteria. Cf. *lipoteichoic acid*

Teichoic acid
Acidic polysaccharide containing either glycerol or ribitol, connected by phosphate diester bonds. Found in the walls of gram-positive bacteria.

Teichoic acid

Teichoic acid is a homopolymer of glycerol, or ribitol linked via phosphodiester bond, which is located in cell wall of gram positive bacteria. It is usually linked to lipoprotein in cytoplasmic membrane, which forms lipoteichoic acid.

It provides structural support for gram positive bacteria.

See also

- Biochemistry

This article is a stub. You can help Wikipedia by expanding it.

teichoic acids

Bacterial polysaccharides that are rich in phosphodiester linkages. They are the major components of the cell walls and membranes of many bacteria.

(12 Dec 1998)

Previous: tegument, tegumental, Teichmann, Teichmann's crystals, teichoic acid
Next: teichopsia, teicoplanin, teil, teinoscope, tek, tektins, tela

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<biochemistry> Compounds formed from teichoic acid linked to glycolipid and found in the walls of most gram-positive bacteria. The lipoteichoic acid of streptococci may function as an adhesin.

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RCB 4/5/2004

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Table 2. List of *A. fulgidus* genes with putative identification. Gene numbers correspond to those in Fig. 2. Percentages represent per cent identities.

AMINO ACID BIOSYNTHESIS		
General		
AF0906	hydantoin utilization protein A (hyuA)	27.4%
Aromatic amino acid family		
AF0228	3-dehydroquinate dehydratase (aroD)	36.8%
AF1497	5-enolpyruvylshikimate 3-phosphate synthase (aroA)	41.5%
AF1603	anthranilate synthase component I (trpE)	43.7%
AF1604	anthranilate synthase component II (trpD)	43.8%
AF1602	anthranilate synthase component II (trpG)	50.0%
AF0227	chorismate mutase/prephenate dehydratase (pheA)	32.2%
AF0670	chorismate synthase (aroC)	55.3%
AF1601	phosphoribosyl anthranilate isomerase (trpF)	37.1%
AF2327	shikimate 5-dehydrogenase (aroE)	43.1%
AF0343	tryptophan repressor binding protein (wrbA)	46.6%
AF1599	tryptophan synthase, subunit alpha (trpA)	39.5%
AF1240	tryptophan synthase, subunit beta (trpB-1)	39.4%
AF1600	tryptophan synthase, subunit beta (trpB-2)	64.1%
Aspartate family		
AF2112	5-methyltetrahydropteroyltriglutamate-homocysteine methyltransferase (metE)	28.1%
AF0882	asparaginase (asnA)	45.9%
AF1439	asparagine synthetase (asnB)	36.9%
AF2366	aspartate aminotransferase (aspB-1)	42.3%
AF2129	aspartate aminotransferase (aspB-2)	45.4%
AF1623	aspartate aminotransferase (aspB-3)	39.4%
AF0409	aspartate aminotransferase (aspB-4)	45.2%
AF1417	aspartate aminotransferase (aspC)	46.2%
AF0700	aspartate kinase (lysC)	49.1%
AF1422	aspartate racemase	48.0%
AF1606	aspartate-semialdehyde dehydrogenase (asd)	60.9%
AF0800	diaminopimelate decarboxylase (lysA)	45.6%
AF0747	diaminopimelate epimerase (dapF)	45.8%
AF0909	dihydrodipicolinate reductase (dapB)	48.6%
AF0910	dihydrodipicolinate synthase (dapA)	51.0%
AF0935	homoserine dehydrogenase (hom)	47.9%
AF0886	S-adenosylhomocysteinase hydrolase (ahcY-1)	31.7%
AF2000	S-adenosylhomocysteinase hydrolase (ahcY-2)	67.3%
AF0051	succinyl-diaminopimelate desuccinylase (dapE-1)	30.5%
AF0904	succinyl-diaminopimelate desuccinylase (dapE-2)	43.8%
AF0551	threonine synthase (thrC-1)	40.5%
AF1316	threonine synthase (thrC-2)	61.0%
Glutamate family		
AF1280	acetylglutamate kinase (argB)	56.1%
AF2288	acetylglutamate kinase, putative	29.0%
AF0080	acetylornithine aminotransferase (argD-1)	48.3%
AF1815	acetylornithine aminotransferase (argD-2)	36.2%
AF0522	acetylornithine deacetylase (argE)	29.4%
AF0883	argininosuccinate lyase (argH)	42.2%
AF2252	argininosuccinate synthetase (argG)	62.0%
AF1147	glutamate N-acetyltransferase (argJ)	47.8%
AF0953	glutamate synthase (gltB)	57.9%
AF0949	glutamine synthetase (glnA)	43.3%
AF2071	N-acetyl-gamma-glutamyl-phosphate reductase (argC)	53.3%
AF1255	ornithine carbamoyltransferase (argF)	51.7%
Pyruvate family		
AF0957	2-isopropylmalate synthase (leuA-1)	53.5%
AF0219	2-isopropylmalate synthase (leuA-2)	53.9%
AF2199	3-isopropylmalate dehydratase, large subunit (leuC)	49.3%
AF0629	3-isopropylmalate dehydratase, small subunit (leuD-1)	56.4%
AF1761	3-isopropylmalate dehydratase, small subunit (leuD-2)	57.1%
AF0628	3-isopropylmalate dehydrogenase (leuB)	59.2%
AF1720	acetolactate synthase, large subunit (ilvB-1)	57.5%
AF1780	acetolactate synthase, large subunit (ilvB-2)	32.1%
AF2015	acetolactate synthase, large subunit (ilvB-3)	34.1%
AF2100	acetolactate synthase, large subunit (ilvB-4)	38.4%
AF1719	acetolactate synthase, small subunit (ilvN)	60.4%
AF1672	acetolactate synthase, small subunit, putative	29.7%
AF0933	branched-chain amino acid aminotransferase (ilvE)	59.0%
AF1014	dihydroxy-acid dehydratase (ilvD)	54.5%
AF1985	keto-acid reductoisomerase (ilvC)	61.8%
Serine family		
AF0813	phosphoglycerate dehydrogenase (serA)	48.8%
AF2138	phosphoserine phosphatase (serB)	50.7%
AF0273	sarcosine oxidase, subunit alpha (soxA)	31.1%
AF0274	sarcosine oxidase, subunit beta (soxB)	26.5%
AF0852	serine hydroxymethyltransferase (glyA)	56.1%
Histidine family		
AF0590	ATP phosphoribosyltransferase (hisG)	31.6%
AF0212	histidinol dehydrogenase (hisD)	51.6%
AF2002	histidinol-phosphate aminotransferase (hisC-1)	39.8%
AF2024	histidinol-phosphate aminotransferase (hisC-2)	36.8%
AF0985	imidazoleglycerol-phosphate dehydrogenase/histidinol-phosphatase (hisB)	42.2%
AF0819	imidazoleglycerol-phosphate synthase, cyclase subunit (hisF)	67.0%
AF2265	imidazoleglycerol-phosphate synthase, subunit H (hisH)	44.4%
AF0509	imidazoleglycerol-phosphate synthase, subunit H, putative	43.2%
AF1950	phosphoribosyl-AMP cyclohydrolase/phosphoribosyl-ATP pyrophosphohydrolase (hisIE)	59.6%
AF0713	phosphoribosylformimino-5-aminoimidazole carboxamide ribotide isomerase (hisA-1)	37.5%
AF0986	phosphoribosylformimino-5-aminoimidazole carboxamide ribotide isomerase (hisA-2)	42.2%
BIOSYNTHESIS OF COFACTORS, PROSTHETIC GROUPS, AND CARRIERS		
General		
AF1865	2,3-dihydroxybenzoate-AMP ligase (entE)	27.2%
AF1070	coenzyme F390 synthetase (ftsA-1)	30.3%
AF1671	coenzyme F390 synthetase (ftsA-2)	31.9%
AF2013	coenzyme F390 synthetase (ftsA-3)	30.4%
AF2151	isochorismatase (entB)	31.2%
Folic acid		
AF1414	dihydropteroate synthase	40.8%
Heme and porphyrin		
AF1648	bacteriochlorophyll synthase, 33 kDa subunit	27.9%
AF0464	bacteriochlorophyll synthase, 43 kDa subunit (chlP-1)	29.7%
AF1023	bacteriochlorophyll synthase, 43 kDa subunit (chlP-2)	31.2%
AF1637	bacteriochlorophyll synthase, 43 kDa subunit (chlP-3)	27.0%
AF0037	cobalamin (5'-phosphate) synthase (cobS-1)	33.9%
AF2323	cobalamin (5'-phosphate) synthase (cobS-2)	34.4%
AF0725	cobalamin biosynthesis precorrin methylase (cbiG)	30.7%
AF0727	cobalamin biosynthesis precorrin-2 methyltransferase (cbiL)	31.5%
AF0726	cobalamin biosynthesis precorrin-3 methylase (cbiF)	49.2%
AF0724	cobalamin biosynthesis precorrin-3 methylase (cbiH)	49.0%
AF0722	cobalamin biosynthesis precorrin-6Y methylase (cbiE)	32.4%
AF0732	cobalamin biosynthesis precorrin-8W decarboxylase (cbiT)	30.8%
AF1336	cobalamin biosynthesis protein (cbiB)	38.4%
AF0723	cobalamin biosynthesis protein (cbiD)	36.3%
AF0728	cobalamin biosynthesis protein (cbiM-1)	51.4%
AF1843	cobalamin biosynthesis protein (cbiM-2)	41.2%
AF0731	cobalt transport ATP-binding protein (cbiO-1)	47.2%
AF1841	cobalt transport ATP-binding protein (cbiO-2)	41.1%
AF0729	cobalt transport protein (cbiN)	56.0%
AF0730	cobalt transport protein (cbiQ-1)	32.6%
AF1842	cobalt transport protein (cbiQ-2)	30.3%
AF1338	cobyric acid synthase (cbiP)	44.5%
AF2229	cobyrinic acid a,c-diamide synthase (cbiA)	42.3%
AF1241	glutamate-1-semialdehyde aminotransferase (hemL)	54.3%
AF1975	glutamyl-tRNA reductase (hemA)	42.7%
AF1594	heme biosynthesis protein (nirH)	25.2%
AF1125	heme biosynthesis protein (nirJ-1)	38.7%
AF2009	heme biosynthesis protein (nirJ-2)	31.8%
AF1593	heme d1 biosynthesis protein (nirD)	29.4%
AF1311	oxygen-independent coproporphyrinogen III oxidase, putative	27.1%
AF1242	porphobilinogen deaminase (hemC)	46.3%
AF1974	porphobilinogen synthase (hemB)	60.4%
AF1784	protoporphyrinogen oxidase (hemK)	33.5%
AF0422	uroporphyrin-III C-methyltransferase (cysG-1)	41.7%
AF1243	uroporphyrin-III C-methyltransferase (cysG-2)	52.5%
AF0116	uroporphyrinogen III synthase (hemD)	27.4%
Menaquinone and ubiquinone		
AF2176	4-hydroxybenzoate octaprenyltransferase (ubiA)	41.6%
AF0404	4-hydroxybenzoate octaprenyltransferase, putative	30.6%
AF2413	coenzyme PQQ synthesis protein (pqqE)	30.5%
AF1191	dihydroxynaphthoic acid synthase (menB)	54.6%
AF1551	octaprenyl-diphosphate synthase (lspB)	33.2%
AF0140	ubiquinone/menaquinone biosynthesis methyltransferase (ubiE)	31.0%
Molybdopterin		
AF2006	molybdenum cofactor biosynthesis protein (moaA)	47.8%
AF0265	molybdenum cofactor biosynthesis protein (moaB)	44.4%
AF2150	molybdenum cofactor biosynthesis protein (moaC)	62.0%
AF0931	molybdenum cofactor biosynthesis protein (moeA-1)	50.8%
AF0930	molybdenum cofactor biosynthesis protein (moeA-2)	44.8%
AF0161	molybdenum cofactor biosynthesis protein (moeA-3)	30.5%
AF0531	molybdenum cofactor biosynthesis protein (moeB)	44.0%
AF1022	molybdenum-pterin-binding protein (mopB)	39.3%
AF1624	molybdopterin converting factor, subunit 1 (moaD)	36.6%
AF2179	molybdopterin converting factor, subunit 2 (moaE)	33.3%
AF2005	molybdopterin-guanine dinucleotide biosynthesis protein A (mobA)	33.2%
AF2253	molybdopterin-guanine dinucleotide biosynthesis protein B (mobB)	40.0%
Pantothenate		
AF1645	pantothenate metabolism flavoprotein (dfp)	42.4%
Riboflavin		
AF0484	GTP cyclohydrolase II (ribA-1)	44.5%
AF2107	GTP cyclohydrolase II (ribA-2)	47.1%
AF1416	riboflavin synthase (ribC)	53.3%
AF2128	riboflavin synthase, subunit beta (ribE)	75.9%
AF2007	riboflavin-specific deaminase (ribG)	43.7%
Thiamine		
AF2075	hydroxyethylthiazole kinase (thiM)	33.6%
AF2208	hydroxymethylpyrimidine phosphate kinase (thiD)	35.5%
AF1695	thiamine biosynthesis protein (apbA)	36.9%
AF2412	thiamine biosynthesis protein (thiC)	60.2%
AF0553	thiamine biosynthesis protein (thiF)	38.1%
AF0088	thiamine biosynthesis protein, putative	28.2%
AF0702	thiamine biosynthetic enzyme (thi1)	50.0%
AF0733	thiamine monophosphate kinase (thiL)	30.4%
AF2074	thiamine phosphate pyrophosphorylase (thiE)	45.5%
Pyridine nucleotides		
AF1000	NH(3)-dependent NAD+ synthetase (nadE)	52.0%
AF1839	nicotinate-nucleotide pyrophosphorylase (nadC)	43.2%
AF1837	quinolinate synthetase (nadA), authentic frameshift	53.9%
CELL ENVELOPE		
Membranes, lipoproteins, and porins		
AF1420	membrane protein	51.8%
AF1354	membrane protein, putative	32.8%
Surface polysaccharides, lipopolysaccharides and antigens		
AF0324	dTDP-glucose 4,6-dehydratase (rfbB)	50.0%
AF0043	first mannosyl transferase (wbaZ-1)	30.0%
AF0606	first mannosyl transferase (wbaZ-2)	29.0%
AF1728	galactosyltransferase	26.9%
AF0044	GDP-D-mannose dehydratase (gmd-1), authentic frameshift	40.7%
AF1142	glucose-1-phosphate cytidylyltransferase (rfbF)	38.6%
AF0242	glucose-1-phosphate thymidylyltransferase (graD-1)	27.7%
AF0325	glucose-1-phosphate thymidylyltransferase (graD-2)	45.2%
AF0321	glycosyl transferase	30.7%
AF0387	glycosyltransferase, putative	33.8%
AF0467	immunogenic protein (bcsp31-1)	34.7%
AF0635	immunogenic protein (bcsp31-2)	44.3%
AF0988	immunogenic protein (bcsp31-3)	28.3%
AF0602	LPS biosynthesis protein, putative	29.6%
AF0617	LPS biosynthesis protein, putative	29.0%
AF0607	LPS glycosyltransferase, putative	29.7%
AF0326	mannose-1-phosphate guanylyltransferase (rfbM), authentic frameshift	42.4%
AF1097	mannose-6-phosphate isomerase/mannose-1-phosphate guanylyl transferase (manC)	43.1%
AF0035	mannosephosphate isomerase, putative	31.3%
AF0046	mannosyltransferase A (mtfA)	38.7%
AF0311	O-antigen biosynthesis protein (rfbC), authentic frameshift	30.6%
AF0458	phosphomannomutase (pmm)	39.5%
AF0595	polysaccharide biosynthesis protein, putative	24.1%
AF0322	rhamnosyl transferase (rfbQ)	27.5%
AF0323	spore coat polysaccharide biosynthesis protein (spsK-2), authentic frameshift	36.3%
AF0620	succinoglycan biosynthesis protein (exoM)	24.8%
AF0361	UDP-glucose 4-epimerase (galE-1)	38.6%
AF2016	UDP-glucose 4-epimerase (galE-2)	30.0%
AF0302	UDP-glucose dehydrogenase (ugd-1)	43.8%
AF0596	UDP-glucose dehydrogenase (ugd-2)	44.1%
Surface structures		
AF1054	flagellin (flaB1-1)	30.0%
AF1055	flagellin (flaB1-2)	31.1%
AF0275	surface layer protein B (slgB-1)	30.8%
AF1413	surface layer protein B (slgB-2)	29.9%
CELLULAR PROCESSES		
General		
AF1040	chemotaxis histidine kinase (cheA)	41.9%
AF1035	chemotaxis histidine kinase, putative	25.3%
AF1036	chemotaxis histidine kinase, putative	30.4%
AF1037	chemotaxis protein methyltransferase (cheR)	33.2%
AF1042	chemotaxis response regulator (cheY)	62.9%
AF1034	methyl-accepting chemotaxis protein (tlpC-1)	27.5%
AF1046	methyl-accepting chemotaxis protein (tlpC-2)	29.6%
AF1041	protein-glutamate methylesterase (cheB)	43.3%
AF1032	purine NTPase, putative	32.2%
AF1044	purine-binding chemotaxis protein (cheW)	40.4%
Cell division		
AF0617	cell division control protein 21 (cdc21)	32.8%
AF1297	cell division control protein 48, AAA family (cdc48-1)	69.1%
AF2098	cell division control protein 48, AAA family (cdc48-2)	62.0%
AF0244	cell division control protein 6, putative	27.5%
AF1285	cell division control protein, AAA family, putative	49.3%
AF0696	cell division inhibitor (minD-1)	55.0%
AF1937	cell division inhibitor (minD-2)	32.8%
AF2051	cell division protein (ftsJ)	40.8%
AF0535	cell division protein (ftsZ-1)	60.4%
AF0570	cell division protein (ftsZ-2)	61.4%
AF0837	cell division protein pelota (pelA)	41.7%
AF1215	cell division protein, putative	32.8%
AF0238	centromere/microtubule-binding protein (cbf5)	58.8%
AF1558	chromosome segregation protein (smc1)	32.8%
AF1822	serine/threonine phosphatase (ppa)	31.9%
Chaperones		
AF1298	small heat shock protein (hsp20-1)	52.3%
AF1971	small heat shock protein (hsp20-2)	38.1%
AF2238	thermosome, subunit alpha (thsA)	70.8%
AF1451	thermosome, subunit beta (thsB)	68.2%
Chromosome-associated protein		
AF0337	archaeal histone A1 (hpyA1-1)	64.6%
AF1493	archaeal histone A1 (hpyA1-2)	69.7%
Detoxification		
AF2173	2-nitropropane dioxygenase (ncd2)	39.7%
AF0270	alkyl hydroperoxide reductase	73.5%
AF1361	arsenate reductase (arsC)	30.5%
AF0550	N-ethylammeline chlorohydrolase (trzA-1)	45.9%
AF0997	N-ethylammeline chlorohydrolase (trzA-2)	44.5%
AF0254	NADH oxidase (noxA-1)	35.1%
AF0395	NADH oxidase (noxA-2)	35.5%
AF0400	NADH oxidase (noxA-3)	40.8%
AF0951	NADH oxidase (noxA-4)	36.7%
AF1858	NADH oxidase (noxA-5)	34.0%
AF0455	NADH oxidase (noxB-1)	43.3%
AF1262	NADH oxidase (noxB-2)	42.9%
AF0226	NADH oxidase (noxC)	38.4%
AF0615	NADH oxidase, putative	25.5%
AF2233	peroxidase / catalase (perA)	62.9%
Protein and peptide secretion		
AF1902	protein translocase, subunit SEC61 alpha (secY)	50.0%
AF0536	protein translocase, subunit SEC61 gamma (secE)	25.0%
AF2062	signal recognition particle receptor (dpa)	54.8%
AF1258	signal recognition particle, subunit SRP19 (srp19)	36.6%
AF0622	signal recognition particle, subunit SRP54 (srp54)	51.2%
AF1791	signal sequence peptidase (sec11)	36.3%
AF1657	signal sequence peptidase (spc21)	47.0%
AF1655	signal sequence peptidase, putative	34.5%
AF0338	type II secretion system protein (gspE-1)	38.5%
AF0659	type II secretion system protein (gspE-2)	38.2%
AF0996	type II secretion system protein (gspE-3)	41.7%
AF1049	type II secretion system protein (gspE-4)	46.5%
CENTRAL INTERMEDIARY METABOLISM		
Degradation of polysaccharides		
AF1207	2-deoxy-D-gluconate 3-dehydrogenase (kduD)	45.3%
AF1795	endoglucanase (celM)	55.4%
Phosphorus compounds		
AF0756	exopolyphosphatase (ppx1)	55.1%
Polyamine biosynthesis		
AF0646	agmatinase (speB)	33.3%
AF2334	spermidine synthase (speE)	37.1%
Polysaccharides - (cytoplasmic)		
AF0599	dolichol phosphate mannose synthase, putative	32.1%
Sulfur metabolism		
AF0288	adenylylsulfate 3-phosphotransferase (cysC)	52.0%
AF1670	adenylylsulfate reductase, subunit A (aprA)	96.0%
AF1669	adenylylsulfate reductase, subunit B (aprB)	97.3%
AF1667	sulfate adenylyltransferase (sat)	28.4%
AF2228	sulfite reductase, desulfoviridin-type subunit gamma (dsvC)	41.3%
AF0423	sulfite reductase, subunit alpha (dsrA)	100.0%
AF0424	sulfite reductase, subunit beta (dsrB)	100.0%
AF0425	sulfite reductase, subunit gamma (dsrD)	97.4%
Other		
AF1706	2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoic acid hydrolase (pchD)	29.4%
AF0675	2-hydroxy-6-oxohepta-2,4-dienoate hydrolase (todF)	26.3%
AF0091	2-hydroxyhepta-2,4-diene-1,7-dioate isomerase (hpcE-1)	44.5%
AF2225	2-hydroxyhepta-2,4-diene-1,7-dioate isomerase (hpcE-2)	66.0%
AF0333	4-hydroxyphenylacetate-3-hydroxylase (hpaA-1)	22.4%
AF0885	4-hydroxyphenylacetate-3-hydroxylase (hpaA-2)	26.0%
AF1027	4-hydroxyphenylacetate-3-hydroxylase (hpaA-3)	21.0%
AF0669	4-oxalocrotonate tautomerase, putative	31.9%
AF0808	glycolate oxidase subunit (glcD)	32.0%
AF2216	methylmalonyl-CoA decarboxylase, biotin carboxyl carrier subunit (mmdC)	36.2%
AF2217	methylmalonyl-CoA decarboxylase, subunit alpha (mmdA)	62.5%
AF1288	methylmalonyl-CoA mutase, subunit alpha (mutB), authentic frameshift	46.1%
AF2219	methylmalonyl-CoA mutase, subunit alpha, C-terminus (mcmA2)	48.7%
AF2215	methylmalonyl-CoA mutase, subunit alpha, N-terminus (mcmA1)	51.2%
AF2099	muconate cycloisomerase II (clcB)	24.9%
AF1425	phosphonopyruvate decarboxylase (bcpC-1)	35.0%
AF1751	phosphonopyruvate decarboxylase (bcpC-2)	48.6%
ENERGY METABOLISM		
Amino acids and amines		
AF1958	2-hydroxyglutaryl-CoA dehydratase, subunit alpha (hgdA)	30.5%

AF1957	2-hydroxyglutaryl-CoA dehydratase, subunit beta (hgdB)	24.4%
AF0130	acetylpolyamine aminohydrolase (aphA)	38.7%
AF2290	acetylpolyamine aminohydrolase, putative	33.3%
AF0991	glutaryl-CoA dehydrogenase (gcdH)	48.7%
AF1323	group II decarboxylase	28.0%
AF2004	group II decarboxylase	46.1%
AF2295	group II decarboxylase	30.5%
AF1665	ornithine cyclodeaminase (arcB)	35.3%
Anaerobic		
AF1145	4-hydroxybutyrate CoA transferase (cat2-1)	46.5%
AF1854	4-hydroxybutyrate CoA transferase (cat2-2)	47.5%
AF0866	glycerol kinase (glpK)	33.8%
AF1328	glycerol-3-phosphate dehydrogenase (glpA)	27.8%
AF0871	glycerol-3-phosphate dehydrogenase (NAD(P)+) (gpsA)	36.3%
AF0020	L-carnitine dehydratase (caiB-1)	33.3%
AF0990	L-carnitine dehydratase (caiB-2)	31.2%
ATP-proton motive force interconversion		
AF1158	ATP synthase, subunit E, putative	47.1%
AF1166	H+-transporting ATP synthase, subunit A (atpA)	67.0%
AF1167	H+-transporting ATP synthase, subunit B (atpB)	72.8%
AF1164	H+-transporting ATP synthase, subunit C (atpC)	37.5%
AF1168	H+-transporting ATP synthase, subunit D (atpD)	47.1%
AF1163	H+-transporting ATP synthase, subunit E (atpE)	36.3%
AF1165	H+-transporting ATP synthase, subunit F (atpF)	45.0%
AF1159	H+-transporting ATP synthase, subunit I (atpI)	30.1%
AF1160	H+-transporting ATP synthase, subunit K (atpK-1)	46.3%
AF1162	H+-transporting ATP synthase, subunit K (atpK-2)	46.3%
Electron transport		
AF2036	cytochrome C oxidase folding protein (coxD)	33.3%
AF0144	cytochrome C oxidase, subunit II (cbaB)	34.2%
AF0142	cytochrome C oxidase, subunit II, putative	38.0%
AF0190	cytochrome C oxidase, subunit II, putative	31.7%
AF1057	cytochrome C-type biogenesis protein (ccdA)	30.7%
AF2192	cytochrome C-type biogenesis protein (nrfE)	36.1%
AF2296	cytochrome oxidase, subunit I (cydA-1)	22.9%
AF2297	cytochrome oxidase, subunit I (cydA-2)	31.5%
AF2046	cytochrome oxidase, subunit I, putative	25.1%
AF0528	cytochrome-c3 hydrogenase, subunit gamma	39.3%
AF0833	desulfoferrodoxin (dfx)	63.0%
AF0344	desulfoferrodoxin, putative	47.3%
AF0287	electron transfer flavoprotein, subunit alpha (etfA)	39.7%
AF0286	electron transfer flavoprotein, subunit beta (etfB)	38.8%
AF1380	F420-nonreducing hydrogenase (vhtA)	34.8%
AF1371	F420-nonreducing hydrogenase (vhtD-1)	30.9%
AF1378	F420-nonreducing hydrogenase (vhtD-2)	33.1%
AF1381	F420-nonreducing hydrogenase (vhtG)	46.1%
AF1824	F420H2:quinone oxidoreductase, 11.2 kDa subunit, putative	24.1%
AF1823	F420H2:quinone oxidoreductase, 16.5 kDa subunit, putative	25.7%
AF1832	F420H2:quinone oxidoreductase, 32 kDa subunit (nuoI)	95.5%
AF1833	F420H2:quinone oxidoreductase, 39 kDa subunit, putative	33.6%
AF1829	F420H2:quinone oxidoreductase, 39.7 kDa subunit, putative	43.8%
AF1831	F420H2:quinone oxidoreductase, 41.2 kDa subunit, putative	34.8%
AF1827	F420H2:quinone oxidoreductase, 43.2 kDa subunit, putative	26.9%
AF1830	F420H2:quinone oxidoreductase, 45 kDa subunit (nuoD)	80.0%
AF1825	F420H2:quinone oxidoreductase, 53.9 kDa subunit (nuoM)	32.1%
AF1826	F420H2:quinone oxidoreductase, 72.4 kDa subunit (nuoL)	33.2%
AF0156	ferredoxin (fdx-1)	45.3%
AF0166	ferredoxin (fdx-2)	49.2%
AF0355	ferredoxin (fdx-3)	53.2%
AF0427	ferredoxin (fdx-4)	56.1%
AF0923	ferredoxin (fdx-5)	56.9%
AF1010	ferredoxin (fdx-6)	44.4%
AF1239	ferredoxin (fdx-7)	29.0%
AF2142	ferredoxin (fdx-8)	38.0%
AF0164	ferredoxin-nitrite reductase (nirA)	29.7%
AF2332	flavodoxin, putative	30.3%
AF0167	flavoprotein (fprA-1)	33.2%
AF1520	flavoprotein (fprA-2)	47.2%
AF0557	flavoprotein reductase	26.2%
AF1463	fumarate reductase, flavoprotein subunit (frdA)	27.0%
AF1536	glutaredoxin (grx-1)	34.3%
AF2145	glutaredoxin (grx-2)	38.8%
AF0663	heterodisulfide reductase, subunit A (hdrA-1)	42.2%
AF1377	heterodisulfide reductase, subunit A (hdrA-2)	46.8%
AF0662	heterodisulfide reductase, subunit A/ methylviologen reducing hydrogenase, subunit delta	34.2%
AF1238	heterodisulfide reductase, subunit A/methylviologen reducing hydrogenase, subunit delta	53.7%
AF1375	heterodisulfide reductase, subunit B (hdrB)	36.0%
AF0271	heterodisulfide reductase, subunit B, putative	35.3%
AF1376	heterodisulfide reductase, subunit C (hdrC)	33.3%
AF0502	heterodisulfide reductase, subunit D, putative	33.8%
AF0809	heterodisulfide reductase, subunit D, putative	100.0%
AF0661	heterodisulfide reductase, subunit E, putative	23.8%
AF0755	heterodisulfide reductase, subunits E and D, putative	31.8%
AF0506	iron-sulfur binding reductase	38.5%
AF1773	iron-sulfur binding reductase	33.3%
AF1998	iron-sulfur binding reductase	29.6%
AF0627	iron-sulfur cluster binding protein	45.5%
AF0688	iron-sulfur cluster binding protein	44.8%
AF1153	iron-sulfur cluster binding protein	27.9%
AF1185	iron-sulfur cluster binding protein	36.7%
AF1263	iron-sulfur cluster binding protein	42.1%
AF2380	iron-sulfur cluster binding protein	35.3%
AF2381	iron-sulfur cluster binding protein	34.4%
AF2409	iron-sulfur cluster binding protein	28.2%
AF0076	iron-sulfur cluster binding protein	32.7%
AF1461	iron-sulfur cluster binding protein, putative	51.0%
AF1436	iron-sulfur flavoprotein (isf-1)	35.7%
AF1519	iron-sulfur flavoprotein (isf-2)	56.8%
AF1896	iron-sulfur flavoprotein (isf-3)	37.1%
AF1372	methylviologen-reducing hydrogenase, subunit alpha (vhuA)	39.4%
AF1374	methylviologen-reducing hydrogenase, subunit delta (vhuD)	41.7%
AF1373	methylviologen-reducing hydrogenase, subunit gamma (vhuG)	38.6%
AF0157	molybdopterin oxidoreductase, iron-sulfur binding subunit	38.6%
AF0174	molybdopterin oxidoreductase, membrane subunit	26.0%
AF0175	molybdopterin oxidoreductase, iron-sulfur binding subunit	42.0%
AF0176	molybdopterin oxidoreductase, molybdopterin binding subunit	32.6%
AF0499	molybdopterin oxidoreductase, iron-sulfur binding subunit	41.5%
AF0500	molybdopterin oxidoreductase, membrane subunit	27.9%
AF1202	molybdopterin oxidoreductase, iron-sulfur binding subunit	35.5%
AF1203	molybdopterin oxidoreductase, molybdopterin binding subunit	30.1%
AF2384	molybdopterin oxidoreductase, molybdopterin binding subunit	34.6%
AF2385	molybdopterin oxidoreductase, iron-sulfur binding subunit	46.9%
AF2386	molybdopterin oxidoreductase, membrane subunit	30.3%
AF0159	molybdopterin oxidoreductase, molybdopterin binding subunit, putative	30.9%
AF2267	NAD(P)H-flavin oxidoreductase	31.4%
AF0131	NAD(P)H-flavin oxidoreductase, putative	28.2%
AF2352	NADH dehydrogenase, subunit 1, putative	28.9%
AF1828	NADH dehydrogenase, subunit 3	24.3%
AF0248	NADH-dependent flavin oxidoreductase	36.7%
AF0342	nigerythrin, putative	33.3%
AF0546	nitrate reductase, gamma subunit (narI)	30.1%
AF0501	nitrate reductase, gamma subunit, putative	29.3%
AF1126	P450 cytochrome, putative	30.5%
AF0463	polyferredoxin (mvhB), authentic frameshift	32.2%
AF1379	quinone-reactive Ni/Fe-hydrogenase B-type cytochrome subunit (hydC)	29.0%
AF0173	reductase, assembly protein	30.0%
AF0547	reductase, iron-sulfur binding subunit	28.3%
AF0867	reductase, putative	33.3%
AF0880	rubredoxin (rd-1)	69.2%
AF1349	rubredoxin (rd-2)	67.9%
AF0832	rubrerythrin (rr1)	45.7%
AF0831	rubrerythrin (rr2)	63.7%
AF1640	rubrerythrin (rr3)	37.8%
AF2312	rubrerythrin (rr4)	41.4%
AF0711	thioredoxin (trx-1)	28.4%
AF0769	thioredoxin (trx-2)	38.5%
AF1284	thioredoxin (trx-3)	52.9%
AF2144	thioredoxin (trx-4)	48.9%
AF1339	ubiquinol-cytochrome C reductase complex, subunit VI requiring protein	60.9%
Fermentation		
AF1779	2-hydroxyacid dehydrogenase, putative	37.6%
AF0469	2-ketoglutarate ferredoxin oxidoreductase, subunit alpha (korA)	52.3%
AF0468	2-ketoglutarate ferredoxin oxidoreductase, subunit beta (korB)	51.2%
AF0470	2-ketoglutarate ferredoxin oxidoreductase, subunit delta (korD)	47.2%
AF0471	2-ketoglutarate ferredoxin oxidoreductase, subunit gamma (korG)	40.0%
AF2053	2-ketoisovalerate ferredoxin oxidoreductase, subunit alpha (vorA)	41.2%
AF2062	2-ketoisovalerate ferredoxin oxidoreductase, subunit beta (vorB)	42.7%
AF2064	2-ketoisovalerate ferredoxin oxidoreductase, subunit delta (vorD)	51.5%
AF2055	2-ketoisovalerate ferredoxin oxidoreductase, subunit gamma (vorG)	45.2%
AF0749	2-oxoacid ferredoxin oxidoreductase, subunit alpha (orA)	33.7%
AF0750	2-oxoacid ferredoxin oxidoreductase, subunit beta (orB)	49.2%
AF1286	acetoin utilization protein, putative	35.1%
AF0197	acetyl-CoA synthetase (acs-1)	27.1%
AF0366	acetyl-CoA synthetase (acs-2)	47.3%
AF0677	acetyl-CoA synthetase (acs-3)	40.9%
AF0975	acetyl-CoA synthetase (acs-4)	42.3%
AF0976	acetyl-CoA synthetase (acs-5)	36.2%
AF1287	acetyl-CoA synthetase (acs-6)	34.3%
AF0024	alcohol dehydrogenase, iron-containing	36.2%
AF0339	alcohol dehydrogenase, iron-containing	37.4%
AF2019	alcohol dehydrogenase, iron-containing	35.7%
AF2389-C	acetyl-CoA synthetase, putative	64.8%
AF2389-N	acetyl-CoA synthetase, putative	59.3%
AF2101	alcohol dehydrogenase, zinc-dependent	34.8%
AF0023	aldehyde ferredoxin oxidoreductase (aor-1)	41.1%
AF0077	aldehyde ferredoxin oxidoreductase (aor-2)	32.6%
AF0340	aldehyde ferredoxin oxidoreductase (aor-3)	38.4%
AF2281	aldehyde ferredoxin oxidoreductase (aor-4)	53.0%
AF0006	corrinoid methyltransferase protein (mtaC-1)	30.7%
AF0011	corrinoid methyltransferase protein (mtaC-2)	29.5%
AF0394	D-lactate dehydrogenase, cytochrome-type (dld)	31.9%
AF0560	formate dehydrogenase (fdhD1), authentic frameshift	32.9%
AF1199	glutaconate CoA-transferase, subunit A (gctA)	31.9%
AF1198	glutaconate CoA-transferase, subunit B (gctB), authentic frameshift	37.0%
AF1489	indolepyruvate ferredoxin oxidoreductase, subunit alpha (iorA)	48.1%
AF2030	indolepyruvate ferredoxin oxidoreductase, subunit beta (iorB)	41.1%
AF0807	L-lactate dehydrogenase, cytochrome-type (lldD)	39.4%
AF0855	L-malate dehydrogenase, NAD+-dependent (mdhA)	40.1%
AF2085	oxaloacetate decarboxylase, biotin carboxyl carrier subunit, putative	38.7%
AF2084	oxaloacetate decarboxylase, sodium ion pump subunit (oadB)	59.8%
AF1252	oxaloacetate decarboxylase, subunit alpha (oadA)	63.3%
AF1701	pyruvate ferredoxin oxidoreductase, subunit alpha (porA)	50.3%
AF1702	pyruvate ferredoxin oxidoreductase, subunit beta (porB)	50.7%
AF1700	pyruvate ferredoxin oxidoreductase, subunit delta (porD)	53.1%
AF1699	pyruvate ferredoxin oxidoreductase, subunit gamma (porG)	50.8%
Gluconeogenesis		
AF0710	phosphoenolpyruvate synthase (ppsA)	61.4%
Glycolysis		
AF1146	3-phosphoglycerate kinase (pgk)	48.8%
AF1132	enolase (eno)	53.9%
AF1732	glyceraldehyde 3-phosphate dehydrogenase (gap)	56.6%
AF1304	triosephosphate isomerase (tpiA)	56.4%
Pentose phosphate pathway		
AF0943	ribose 5-phosphate isomerase (rpi)	48.9%
Sugars		
AF0356	carbohydrate kinase, pfkB family	31.3%
AF0401	carbohydrate kinase, pfkB family	34.1%
AF1324	carbohydrate kinase, FGGY family	27.1%
AF1752	carbohydrate kinase, FGGY family	29.3%
AF0861	D-arabino 3-hexulose 6-phosphate formaldehyde lyase (hps-1)	30.6%
AF1305	D-arabino 3-hexulose 6-phosphate formaldehyde lyase (hps-2)	44.2%
AF0480	fuculose-1-phosphate aldolase (fucA)	31.8%
TCA cycle		
AF1963	aconitase (acn)	57.1%
AF1340	citrate synthase (citZ)	50.3%
AF1098	fumarase (fum-1)	49.1%
AF1099	fumarase (fum-2)	53.4%
AF0647	isocitrate dehydrogenase, NADP (icd)	57.2%
AF1727	malate oxidoreductase (mae)	52.3%
AF0681	succinate dehydrogenase, flavoprotein subunit A (sdhA)	48.2%
AF0682	succinate dehydrogenase, iron-sulfur subunit B (sdhB)	51.3%
AF0683	succinate dehydrogenase, subunit C (sdhC)	36.6%
AF0684	succinate dehydrogenase, subunit D (sdhD)	25.9%
AF1539	succinyl-CoA synthetase, alpha subunit (sucD-1)	56.9%
AF2185	succinyl-CoA synthetase, alpha subunit (sucD-2)	63.5%
AF1540	succinyl-CoA synthetase, beta subunit (sucC-1)	51.3%
AF2186	succinyl-CoA synthetase, beta subunit (sucC-2)	49.8%

FATTY ACID AND PHOSPHOLIPID METABOLISM

General		
AF1736	3-hydroxy-3-methylglutaryl-coenzyme A reductase (mvaA)	57.1%
AF0017	3-hydroxyacyl-CoA dehydrogenase (hbd-1)	41.1%
AF0285	3-hydroxyacyl-CoA dehydrogenase (hbd-2)	55.8%
AF0434	3-hydroxyacyl-CoA dehydrogenase (hbd-3)	40.7%
AF1025	3-hydroxyacyl-CoA dehydrogenase (hbd-4)	45.6%
AF1122	3-hydroxyacyl-CoA dehydrogenase (hbd-5)	45.2%
AF1177	3-hydroxyacyl-CoA dehydrogenase (hbd-6)	35.8%
AF1190	3-hydroxyacyl-CoA dehydrogenase (hbd-7)	46.5%
AF1206	3-hydroxyacyl-CoA dehydrogenase (hbd-8)	36.3%
AF2017	3-hydroxyacyl-CoA dehydrogenase (hbd-9)	35.4%
AF2273	3-hydroxyacyl-CoA dehydrogenase (hbd-10)	39.4%
AF0018	3-ketoacyl-CoA thiolase (acaB-1)	41.0%
AF0034	3-ketoacyl-CoA thiolase (acaB-2)	38.3%
AF0133	3-ketoacyl-CoA thiolase (acaB-3)	32.3%
AF0134	3-ketoacyl-CoA thiolase (acaB-4)	32.5%
AF0201	3-ketoacyl-CoA thiolase (acaB-5)	26.9%
AF0202	3-ketoacyl-CoA thiolase (acaB-6)	33.5%
AF0283	3-ketoacyl-CoA thiolase (acaB-7)	42.0%
AF0438	3-ketoacyl-CoA thiolase (acaB-8)	42.4%
AF0967	3-ketoacyl-CoA thiolase (acaB-9)	33.7%
AF0968	3-ketoacyl-CoA thiolase (acaB-10)	28.0%
AF1291	3-ketoacyl-CoA thiolase (acaB-11)	40.1%
AF2416	3-ketoacyl-CoA thiolase (acaB-12)	49.9%
AF1028	3-ketoacyl-CoA thiolase (fadA-1)	38.8%
AF1197	3-ketoacyl-CoA thiolase (fadA-2)	47.2%
AF2243	3-ketoacyl-CoA thiolase (fadA-3)	40.3%
AF0033	acyl carrier protein synthase (acaA-1)	28.6%
AF2415	acyl carrier protein synthase (acaA-2)	58.7%
AF0199	acyl-CoA dehydrogenase (acd-1)	35.9%
AF0436	acyl-CoA dehydrogenase (acd-2)	44.1%
AF0498	acyl-coA dehydrogenase (acd-3)	22.9%
AF0671	acyl-CoA dehydrogenase (acd-4)	37.9%
AF0845	acyl-CoA dehydrogenase (acd-5)	44.6%
AF0964	acyl-CoA dehydrogenase (acd-6)	35.8%
AF1026	acyl-CoA dehydrogenase (acd-7)	42.6%
AF1141	acyl-CoA dehydrogenase (acd-8)	43.2%
AF1293	acyl-CoA dehydrogenase (acd-9)	45.8%
AF2057	acyl-CoA dehydrogenase (acd-10)	44.6%
AF2244	acyl-CoA dehydrogenase (acd-11)	42.6%
AF2275	acyl-CoA dehydrogenase (acd-12)	38.9%
AF1175	acyl-CoA dehydrogenase, short chain-specific (acdS)	30.1%
AF0818	acylphosphatase (acyP)	36.8%
AF0868	alkyldihydroxyacetonephosphate synthase	33.6%
AF2286	bifunctional short chain isoprenyl diphosphate synthase (idsA)	42.7%
AF0220	biotin carboxylase (acc)	59.1%
AF0865	carboxylesterase (est-1)	27.1%
AF1537	carboxylesterase (est-2)	29.0%
AF2336	carboxylesterase (est-3)	30.4%
AF1716	carboxylesterase (estA)	40.4%
AF1744	CDP-diacylglycerol–glycerol-3-phosphate 3-phosphatidyltransferase (pgsA-2)	26.7%
AF1143	CDP-diacylglycerol–glycerol-3-phosphate-3-phosphatidyltransferase (pgsA-1)	27.0%
AF2044	CDP-diacylglycerol–serine O-phosphatidyltransferase (pssA)	36.6%
AF0435	enoyl-CoA hydratase (fad-1)	47.6%
AF0685	enoyl-CoA hydratase (fad-2)	39.9%
AF0963	enoyl-CoA hydratase (fad-3)	48.6%
AF1641	enoyl-CoA hydratase (fad-4)	41.7%
AF2429	enoyl-CoA hydratase (fad-5)	34.7%
AF1763	lipase, putative	33.5%
AF0089	long-chain-fatty-acid–CoA ligase (fadD-1)	31.9%
AF0200	long-chain-fatty-acid–CoA ligase (fadD-2)	34.8%
AF0687	long-chain-fatty-acid–CoA ligase (fadD-3)	31.1%
AF0840	long-chain-fatty-acid–CoA ligase (fadD-4)	38.1%
AF1029	long-chain-fatty-acid–CoA ligase (fadD-5)	37.8%
AF1510	long-chain-fatty-acid–CoA ligase (fadD-6)	36.0%
AF1772	long-chain-fatty-acid–CoA ligase (fadD-7)	38.7%
AF1932	long-chain-fatty-acid–CoA ligase (fadD-8)	31.0%
AF2368	long-chain-fatty-acid–CoA ligase (fadD-9)	38.7%
AF1753	lysophospholipase	33.5%
AF0196	medium-chain acyl-CoA ligase (alkK-1)	34.6%
AF0262	medium-chain acyl-CoA ligase (alkK-2)	38.6%
AF0672	medium-chain acyl-CoA ligase (alkK-3)	31.0%
AF1261	medium-chain acyl-CoA ligase (alkK-4)	42.7%
AF2033	medium-chain acyl-CoA ligase (alkK-5)	33.5%
AF2289	mevalonate kinase (mvk)	40.6%
AF1794	myo-inositol-1-phosphate synthase (ino1)	32.2%
AF2045	phosphatidylserine decarboxylase (psd2)	42.5%
AF1674	sn-glycerol-1-phosphate dehydrogenase (gldA)	44.0%

AUTOTROPHIC METABOLISM

General		
AF1100	acetyl-CoA decarbonylase/synthase, subunit alpha (cdhA-1)	50.4%
AF2397	acetyl-CoA decarbonylase/synthase, subunit alpha (cdhA-2)	54.0%
AF0379	acetyl-CoA decarbonylase/synthase, subunit beta (cdhC)	62.7%
AF0377	acetyl-CoA decarbonylase/synthase, subunit delta (cdhD)	57.4%
AF1101	acetyl-CoA decarbonylase/synthase, subunit epsilon (cdhB-1)	40.0%
AF2398	acetyl-CoA decarbonylase/synthase, subunit epsilon (cdhB-2)	38.9%
AF0376	acetyl-CoA decarbonylase/synthase, subunit gamma (cdhE)	55.4%
AF1849	carbon monoxide dehydrogenase, catalytic subunit (cooS)	39.9%
AF0950	carbon monoxide dehydrogenase, iron sulfur subunit (cooF)	38.9%
AF1535	ferredoxin-thioredoxin reductase, catalytic subunit (ftrB)	38.6%
AF2073	formylmethanofuran:tetrahydromethanopterin formyltransferase (ftr-1)	46.0%
AF2207	formylmethanofuran:tetrahydromethanopterin formyltransferase (ftr-2)	68.4%

AF1935	N5,N10-methenyltetrahydromethanopterin cyclohydrolase (mch)	97.3%
AF0714	N5,N10-methylenetetrahydromethanopterin dehydrogenase (mtd)	61.8%
AF1066	N5,N10-methylenetetrahydromethanopterin reductase (mer-1)	59.1%
AF1196	N5,N10-methylenetetrahydromethanopterin reductase (mer-2)	37.4%
AF0009	N5-methyltetrahydromethanopterin:coenzyme M methyltransferase (mtr)	42.1%
AF1687	ribulose bisphosphate carboxylase, large subunit (rbcL-1)	40.6%
AF1638	ribulose bisphosphate carboxylase, large subunit (rbcL-2)	44.9%
AF1930	tungsten formylmethanofuran dehydrogenase, subunit A (fwdA)	48.9%
AF1650	tungsten formylmethanofuran dehydrogenase, subunit B (fwdB-1)	37.0%
AF1929	tungsten formylmethanofuran dehydrogenase, subunit B (fwdB-2)	49.4%
AF1931	tungsten formylmethanofuran dehydrogenase, subunit C (fwdC)	44.1%
AF1651	tungsten formylmethanofuran dehydrogenase, subunit D (fwdD-1)	32.6%
AF1928	tungsten formylmethanofuran dehydrogenase, subunit D (fwdD-2)	52.6%
AF0177	tungsten formylmethanofuran dehydrogenase, subunit E (fwdE)	29.7%
AF1644	tungsten formylmethanofuran dehydrogenase, subunit F (fwdF)	38.2%
AF1649	tungsten formylmethanofuran dehydrogenase, subunit G (fwdG)	45.6%

PURINES, PYRIMIDINES, NUCLEOSIDES, AND NUCLEOTIDES

2'-Deoxyribonucleotide metabolism

AF1108	deoxycytidine triphosphate deaminase, putative	38.1%
AF1664	ribonucleotide reductase (nrd)	59.7%
AF1654	thioredoxin reductase (trxB)	45.2%
AF2047	thymidylate synthase, putative	33.1%

Nucleotide and nucleoside interconversions

AF0676	5'-nucleotidase (nt5)	30.9%
AF0676	adenylate kinase (adk)	56.1%
AF1900	cytidylate kinase (cmk)	48.6%
AF0767	nucleoside diphosphate kinase (ndk)	56.4%
AF0061	thymidylate kinase (tmk)	34.9%
AF1308	thymidylate kinase, putative	26.3%
AF2042	uridylate kinase (pyrH)	53.6%

Purine ribonucleotide biosynthesis

AF2242	adenylosuccinate lyase (purB)	52.3%
AF0841	adenylosuccinate synthetase (purA)	70.8%
AF0873	amidophosphoribosyltransferase (purF)	55.8%
AF0253	GMP synthase (guaA-1)	59.8%
AF1320	GMP synthase (guaA-2)	49.4%
AF1811	inosine monophosphate cyclohydrolase	38.3%
AF0847	inosine monophosphate dehydrogenase (guaB-1)	41.8%
AF2118	inosine monophosphate dehydrogenase (guaB-2)	31.9%
AF1259	inosine monophosphate dehydrogenase, putative	51.6%
AF1157	phosphoribosylamine–glycine ligase (purD)	40.9%
AF1271	phosphoribosylaminoimidazole carboxylase (purE)	42.8%
AF1272	phosphoribosylaminoimidazolesuccinocarboxamide synthase (purC)	34.7%
AF1693	phosphoribosylformylglycinamidine cyclo-ligase (purM)	53.8%
AF1260	phosphoribosylformylglycinamidine synthase I (purQ)	40.9%
AF1940	phosphoribosylformylglycinamidine synthase II (purL)	41.5%
AF0589	ribose-phosphate pyrophosphokinase (prsA-1)	35.0%
AF1419	ribose-phosphate pyrophosphokinase (prsA-2)	41.1%

Pyrimidine ribonucleotide biosynthesis

AF0106	aspartate carbamoyltransferase, catalytic subunit (pyrB)	60.7%
AF0107	aspartate carbamoyltransferase, regulatory subunit (pyrI)	48.2%
AF1274	carbamoyl-phosphate synthase, large subunit (carB)	65.1%
AF1273	carbamoyl-phosphate synthase, small subunit (carA)	55.2%
AF0252	CTP synthase (pyrG)	58.3%
AF2250	dihydroorotase (pyrC)	37.2%
AF0745	dihydroorotase dehydrogenase (pyrD)	44.8%
AF1741	orotate phosphoribosyl transferase (pyrE)	49.0%
AF0386	orotate phosphoribosyl transferase, putative	39.0%

Salvage of nucleosides and nucleotides

AF0240	adenine deaminase (adeC)	39.5%
AF1764	dCMP deaminase, putative	39.0%
AF1788	methylthioadenosine phosphorylase (mtaP)	40.0%
AF1341	thymidine phosphorylase (deoA-1)	46.7%
AF1342	thymidine phosphorylase (deoA-2)	40.7%
AF0239	xanthine-guanine phosphoribosyltransferase (gptA-1)	25.7%
AF1789	xanthine-guanine phosphoribosyltransferase (gptA-2)	28.2%

REGULATORY FUNCTIONS

AF1959	(R)-hydroxyglutaryl-CoA dehydratase activator (hgdC)	51.2%
AF0168	arsenical resistance operon repressor, putative	36.7%
AF2204	arylsulfatase regulatory protein, putative	29.9%
AF0074	biotin operon repressor/biotin-[acetyl CoA carboxylase] ligase (birA)	36.6%
AF1724	dinitrogenase reductase activating glycohydrolase (draG)	37.9%
AF2232	ferric uptake regulation protein (fur)	25.8%
AF1785	iron-dependent repressor	42.0%
AF2395	iron-dependent repressor	40.0%
AF0245	iron-dependent repressor (desR)	28.2%
AF1984	iron-dependent repressor (troR)	28.3%
AF2430	lacZ expression regulatory protein (icc)	29.6%
AF1622	leucine responsive regulatory protein (lrp)	29.1%
AF0673	mercuric resistance operon regulatory protein (merR)	37.6%
AF2425	methanol dehydrogenase regulatory protein (moxR)	48.3%
AF1475	mitochondrial benzodiazepine receptor/sensory transduction protein	38.4%
AF0198	monoamine oxidase regulatory protein, putative	41.7%
AF1933	monoamine oxidase regulatory protein, putative	38.9%
AF0978	nitrogen regulatory protein P-II (glnB-1)	61.7%
AF1747	nitrogen regulatory protein P-II (glnB-2)	58.0%
AF1750	nitrogen regulatory protein P-II (glnB-3)	60.7%
AF0331	pheromone shutdown protein (traB)	40.5%
AF1797	phosphate regulatory protein, putative	30.7%
AF0621	protease synthase and sporulation regulator Pai1, putative	52.4%
AF1627	repressor protein	59.1%
AF1793	repressor protein	54.5%
AF0449	response regulator	38.1%
AF1063	response regulator	36.3%
AF1256	response regulator	42.5%
AF1384	response regulator	44.7%
AF1473	response regulator	32.5%
AF1898	response regulator	48.7%
AF2249	response regulator	44.8%
AF2419	response regulator	37.9%
AF0004	RNase L inhibitor	54.5%
AF0021	signal-transducing histidine kinase	26.1%
AF0208	signal-transducing histidine kinase	27.9%
AF0450	signal-transducing histidine kinase	32.4%
AF0770	signal-transducing histidine kinase	26.9%
AF0893	signal-transducing histidine kinase	28.7%
AF1184	signal-transducing histidine kinase	29.8%
AF1452	signal-transducing histidine kinase	28.5%
AF1467	signal-transducing histidine kinase	37.4%
AF1472	signal-transducing histidine kinase	30.4%
AF1483	signal-transducing histidine kinase	27.7%
AF1515	signal-transducing histidine kinase	32.0%
AF1639	signal-transducing histidine kinase	29.9%
AF1721	signal-transducing histidine kinase	34.6%
AF2109	signal-transducing histidine kinase	31.6%
AF0881	signal-transducing histidine kinase, authentic frameshift	26.5%
AF0277	signal-transducing histidine kinase, putative	29.8%
AF0410	signal-transducing histidine kinase, putative	27.1%
AF0448	signal-transducing histidine kinase, putative	26.1%
AF1620	signal-transducing histidine kinase, putative	26.2%
AF2032	signal-transducing histidine kinase, putative	22.5%
AF2420	signal-transducing histidine kinase, putative	28.4%
AF0442	succinoglycan biosynthesis regulator (exsB)	37.2%
AF1516	sugar fermentation stimulation protein (sfsA)	31.0%
AF1270	transcriptional regulatory protein, ArsR family	35.4%
AF1544	transcriptional regulatory protein, ArsR family	32.3%
AF1863	transcriptional regulatory protein, ArsR family	34.9%
AF2136	transcriptional regulatory protein, ArsR family	39.8%
AF0439	transcriptional regulatory protein, AsnC family	29.8%
AF0474	transcriptional regulatory protein, AsnC family	51.0%
AF0584	transcriptional regulatory protein, AsnC family	35.3%
AF1121	transcriptional regulatory protein, AsnC family	35.8%
AF1148	transcriptional regulatory protein, AsnC family	32.6%
AF1404	transcriptional regulatory protein, AsnC family	45.1%
AF1448	transcriptional regulatory protein, AsnC family	30.6%
AF1723	transcriptional regulatory protein, AsnC family	46.4%
AF1743	transcriptional regulatory protein, AsnC family	34.9%
AF2127	transcriptional regulatory protein, LysR family	30.8%
AF0114	transcriptional regulatory protein, putative	35.6%
AF1968	transcriptional regulatory protein, Rok family	32.9%
AF0112	transcriptional regulatory protein, Sir2 family	38.9%
AF1676	transcriptional regulatory protein, Sir2 family	40.6%
AF1817	transcriptional regulatory protein, TetR family	24.5%
AF0363	transcriptional repressor (cinR)	27.6%

REPLICATION

DNA replication, restriction, modification, recombination, and repair

AF2117	3-methyladenine DNA glycosylase (alkA)	30.0%
AF2060	activator 1, replication factor C, 35 KDa subunit	66.3%
AF1195	activator 1, replication factor C, 53 KDa subunit	43.7%
AF0465	DNA gyrase, subunit A (gyrA)	48.4%
AF0530	DNA gyrase, subunit B (gyrB)	58.4%
AF1388	DNA helicase, putative	46.8%
AF1960	DNA helicase, putative	32.7%
AF0623	DNA ligase (lig)	44.4%
AF1725	DNA ligase, putative	32.7%
AF0497	DNA polymerase B1 (polB)	45.1%
AF0693	DNA polymerase B2 (boxA), authentic frameshift	32.3%
AF0972	DNA polymerase III, subunit epsilon (dnaQ)	31.9%
AF2277	DNA polymerase, bacteriophage-type	36.9%
AF0742	DNA primase, putative	26.8%
AF0264	DNA repair protein RAD2 (rad2)	44.4%
AF0358	DNA repair protein RAD25	32.5%
AF1031	DNA repair protein RAD32 (rad32)	37.6%
AF0993	DNA repair protein RAD51 (radA)	59.3%
AF2096	DNA repair protein REC	40.0%
AF2418	DNA repair protein, putative	28.9%
AF1806	DNA topoisomerase I (topA)	36.2%
AF0940	DNA topoisomerase VI, subunit A (top6A)	39.8%
AF0652	DNA topoisomerase VI, subunit B (top6B)	43.9%
AF1692	endonuclease III (nth)	44.3%
AF0580	exodeoxyribonuclease III (xthA)	41.3%
AF2314	methylated-DNA-protein-cysteine methyltransferase (ogt)	55.3%
AF1409	modification methylase, type III R/M system	31.4%
AF1234	mutator protein MutT (mutT)	63.6%
AF2200	mutator protein MutT, putative	42.0%
AF0335	proliferating-cell nuclear antigen (pol30)	33.7%
AF0694	replication control protein A, putative	30.2%
AF1024	reverse gyrase (top-RG)	40.7%
AF0621	ribonuclease HIII (rnhB)	39.3%
AF1715	type I restriction-modification enzyme, M subunit, authentic frameshift	63.0%
AF1708	type I restriction-modification enzyme, R subunit	38.2%
AF1710	type I restriction-modification enzyme, S subunit	33.0%

TRANSCRIPTION

DNA-dependent RNA polymerase

AF1888	DNA-directed RNA polymerase, subunit A' (rpoA1)	63.6%
AF1889	DNA-directed RNA polymerase, subunit A'' (rpoA2)	55.7%
AF1887	DNA-directed RNA polymerase, subunit B' (rpoB1)	65.3%
AF1886	DNA-directed RNA polymerase, subunit B'' (rpoB2)	57.1%
AF2282	DNA-directed RNA polymerase, subunit D (rpoD)	34.6%
AF1117	DNA-directed RNA polymerase, subunit E' (rpoE1)	48.4%
AF1116	DNA-directed RNA polymerase, subunit E'' (rpoE2)	40.0%
AF1885	DNA-directed RNA polymerase, subunit H (rpoH)	59.5%
AF1131	DNA-directed RNA polymerase, subunit K (rpoK)	61.5%
AF0207	DNA-directed RNA polymerase, subunit L (rpoL)	42.0%
AF1130	DNA-directed RNA polymerase, subunit N (rpoN)	58.8%

Transcription factors

AF1813	TBP-interacting protein TIP49	45.7%
AF1299	transcription initiation factor IIB	60.4%
AF0373	transcription initiation factor IID	59.4%
AF0757	transcription initiation factor IIE, subunit alpha, putative	23.5%
AF1891	transcription termination-antitermination factor NusA, putative	48.9%
AF1235	transcription-associated protein TFIIS	59.0%

RNA processing

AF1783	dimethyladenosine transferase (ksgA)	44.7%
AF2067	fibrillarin (fib)	49.3%
AF0482	mRNA 3'-end processing factor, putative	55.5%
AF0632	mRNA 3'-end processing factor, putative	39.1%
AF2361	mRNA 3'-end processing factor, putative	30.5%
AF2399	rRNA methylase, putative	36.4%
AF0362	snRNP, putative	32.0%
AF0875	snRNP, putative	35.7%

TRANSLATION

Amino acyl tRNA synthetases

AF2255	alanyl-tRNA synthetase (alaS)	47.1%
AF0894	arginyl-tRNA synthetase (argS)	48.8%
AF0920	aspartyl-tRNA synthetase (aspS)	62.5%
AF0411	cysteinyl-tRNA synthetase (cysS)	46.1%
AF0260	glutamyl-tRNA synthetase (glX)	44.9%
AF0916	glycyl-tRNA synthetase (glyS)	51.2%
AF1642	histidyl-tRNA synthetase (hisS)	46.0%
AF0633	isoleucyl-tRNA synthetase (ileS)	48.9%
AF2421	leucyl-tRNA synthetase (leuS)	49.7%
AF1218	lysyl-tRNA synthetase (lysS)	43.6%
AF1463	methionyl-tRNA synthetase (metS)	45.2%
AF1955	phenylalanyl-tRNA synthetase, subunit alpha (pheS)	44.4%
AF1424	phenylalanyl-tRNA synthetase, subunit beta (pheT)	42.6%
AF1609	prolyl-tRNA synthetase (proS)	56.8%
AF2035	seryl-tRNA synthetase (serS)	45.4%
AF0548	threonyl-tRNA synthetase (thrS)	46.9%
AF1694	tryptophanyl-tRNA synthetase (trpS)	52.4%
AF0776	tyrosyl-tRNA synthetase (tyrS)	57.6%
AF2224	valyl-tRNA synthetase (valS)	54.5%

Degradation of proteins, peptides, and glycopeptides

AF1976	26S protease regulatory subunit 4	66.0%
AF1653	alkaline serine protease (aprM)	44.5%
AF0578	aminopeptidase, putative	27.8%
AF0364	ATP-dependent protease La (lon)	36.6%
AF1946	cysteine proteinase, putative	36.2%
AF1281	intracellular protease (pfpI)	56.0%
AF1112	O-sialoglycoprotein endopeptidase (gcp)	57.6%
AF0665	O-sialoglycoprotein endopeptidase, putative	35.8%
AF2086	protease inhibitor, putative	37.0%
AF0490	proteasome, subunit alpha (psmA)	60.8%
AF0481	proteasome, subunit beta (psmB)	58.3%
AF2034	X-pro aminopeptidase (pepQ)	34.8%

Protein modification

AF0656	antibiotic maturation protein (pmbA)	32.7%
AF0378	CODH nickel-insertion accessory protein (cooC-1)	35.7%
AF1685	CODH nickel-insertion accessory protein (cooC-2)	47.4%
AF1615	cofactor modifying protein (cmo)	27.2%
AF2195	deoxyhypusine synthase (dys1-1)	32.6%
AF2300	deoxyhypusine synthase (dys1-2)	34.9%
AF0381	diphthine synthase (dph5)	40.8%
AF2324	fmu and fmv protein	40.0%
AF1367	hydrogenase expression/formation protein (hypA)	40.4%
AF1368	hydrogenase expression/formation protein (hypB)	54.4%
AF1369	hydrogenase expression/formation protein (hypC)	40.5%
AF1370	hydrogenase expression/formation protein (hypD)	46.0%
AF1365	hydrogenase expression/formation protein (hypE)	51.5%
AF1366	hydrogenase expression/formation regulatory protein (hypF)	45.1%
AF0036	L-isoaspartyl protein carboxyl methyltransferase (pcm-1)	60.7%
AF2322	L-isoaspartyl protein carboxyl methyltransferase (pcm-2)	59.3%
AF1840	methionyl aminopeptidase (map)	48.6%
AF1989	peptidyl-prolyl cis-trans isomerase (slyD)	34.4%
AF0853	proliferating-cell nucleolar antigen P120, putative	35.7%
AF2039	proliferating-cell nucleolar antigen P120, putative	44.2%
AF1449	pyruvate formate-lyase 2 (pflD)	37.8%
AF1450	pyruvate formate-lyase 2 activating enzyme (pflC)	38.8%
AF0117	pyruvate formate-lyase activating enzyme (act-1)	25.5%
AF0918	pyruvate formate-lyase activating enzyme (act-2)	42.3%
AF1330	pyruvate formate-lyase activating enzyme (act-3)	45.8%
AF2278	pyruvate formate-lyase activating enzyme (act-4)	42.5%
AF1961	pyruvate formate-lyase activating enzyme (pflX)	50.2%
AF0380	transmembrane oligosaccharyl transferase, putative	27.8%
AF0329	transmembrane oligosaccharyl transferase, putative	29.3%

Ribosomal proteins: synthesis and modification

AF1490	LSU ribosomal protein L1P (rpl1P)	48.6%
AF1922	LSU ribosomal protein L2P (rpl2P)	60.4%
AF1925	LSU ribosomal protein L3P (rpl3P)	56.5%
AF1924	LSU ribosomal protein L4P (rpl4P)	56.4%
AF1912	LSU ribosomal protein L5P (rpl5P)	51.7%
AF1909	LSU ribosomal protein L6P (rpl6P)	53.7%
AF0764	LSU ribosomal protein L7AE (rpl7AE)	60.7%
AF1491	LSU ribosomal protein L10E (rpl10E)	45.6%
AF0638	LSU ribosomal protein L11P (rpl11P)	67.8%
AF1492	LSU ribosomal protein L12A (rpl12A)	76.0%
AF1128	LSU ribosomal protein L13P (rpl13P)	47.4%
AF1915	LSU ribosomal protein L14P (rpl14P)	66.7%
AF2319	LSU ribosomal protein L15E (rpl15E)	70.3%
AF1903	LSU ribosomal protein L15P (rpl15P)	53.8%
AF1127	LSU ribosomal protein L18E (rpl18E)	53.8%
AF1906	LSU ribosomal protein L18P (rpl18P)	57.8%
AF1907	LSU ribosomal protein L19E (rpl19E)	55.5%
AF1529	LSU ribosomal protein L21E (rpl21E)	53.2%
AF1920	LSU ribosomal protein L22P (rpl22P)	55.2%
AF1923	LSU ribosomal protein L23P (rpl23P)	55.6%
AF0537	LSU ribosomal protein L24A (rpl24A)	51.4%
AF0766	LSU ribosomal protein L24E (rpl24E)	66.1%
AF1914	LSU ribosomal protein L24P (rpl24P)	57.8%
AF1918	LSU ribosomal protein L29P (rpl29P)	44.6%
AF1890	LSU ribosomal protein L30E (rpl30E)	41.7%
AF1904	LSU ribosomal protein L30P (rpl30P)	55.9%
AF2066	LSU ribosomal protein L31E (rpl31E)	50.6%
AF1908	LSU ribosomal protein L32E (rpl32E)	51.2%
AF0057	LSU ribosomal protein L37AE (rpl37AE)	47.8%
AF0874	LSU ribosomal protein L37E (rpl37E)	57.9%
AF2067	LSU ribosomal protein L39E (rpl39E)	56.9%
AF1430	LSU ribosomal protein L40E (rpl40E)	73.3%
AF1333	LSU ribosomal protein L44E (rpl44E)	46.8%
AF2064	LSU ribosomal protein LXA (rplXA)	53.8%
AF0739	ribosomal protein S18 alanine acetyltransferase	38.5%
AF2303	ribosomal protein S6 modification protein (rimK)	32.2%
AF1133	SSU ribosomal protein S2P (rps2P)	58.3%
AF1919	SSU ribosomal protein S3P (rps3P)	50.0%
AF1913	SSU ribosomal protein S4E (rps4E)	48.9%
AF2284	SSU ribosomal protein S4P (rps4P)	59.1%
AF1905	SSU ribosomal protein S5P (rps5P)	60.0%
AF0511	SSU ribosomal protein S6E (rps6E)	50.8%
AF1893	SSU ribosomal protein S7P (rps7P)	59.6%
AF2152	SSU ribosomal protein S8E (rps8E)	61.6%
AF1910	SSU ribosomal protein S8P (rps8E)	64.6%
AF1129	SSU ribosomal protein S9P (rps9P)	59.5%
AF0938	SSU ribosomal protein S10P (rps10P)	71.0%
AF2283	SSU ribosomal protein S11P (rps11P)	71.1%
AF1892	SSU ribosomal protein S12P (rps12P)	74.1%
AF2285	SSU ribosomal protein S13P (rps13P)	52.1%
AF1911	SSU ribosomal protein S14P (rps14P)	61.5%
AF0801	SSU ribosomal protein S15P (rps15P)	62.0%
AF0911	SSU ribosomal protein S17E (rps17E)	52.6%
AF1916	SSU ribosomal protein S17P (rps17P)	59.0%
AF2069	SSU ribosomal protein S19E (rps19E)	64.2%
AF1921	SSU ribosomal protein S19P (rps19P)	60.9%
AF1114	SSU ribosomal protein S24E (rps24E)	40.2%
AF1113	SSU ribosomal protein S27AE (rps27AE)	60.0%
AF1334	SSU ribosomal protein S27E (rps27E)	49.0%
AF0765	SSU ribosomal protein S28E (rps28E)	55.6%
AF2320	SSU ribosomal protein S3AE (rps3AE)	38.9%

tRNA modification

AF0588	archaeosine tRNA-ribosyltransferase (tgtA)	52.0%
AF1954	Glu-tRNA amidotransferase, subunit A (gatA-1)	38.6%
AF2329	Glu-tRNA amidotransferase, subunit A (gatA-2)	53.5%
AF1440	Glu-tRNA amidotransferase, subunit B (gatB-1)	54.7%
AF2116	Glu-tRNA amidotransferase, subunit B (gatB-2)	46.4%

AF2328	Glu-tRNA amidotransferase, subunit C (gatC)	35.1%
AF0815	N2,N2-dimethylguanosine tRNA methyltransferase (trm1)	38.2%
AF1730	pseudouridylate synthase I (truA)	37.4%
AF1485	queuine tRNA-ribosyltransferase (tgtB)	44.1%
AF0493	ribonuclease PH (rph)	30.8%
AF0900	tRNA intron endonuclease (endA)	41.8%
AF2156	tRNA nucleotidyltransferase (cca)	43.9%
Translation factors		
AF2350	ATP-dependent RNA helicase HepA, putative	31.5%
AF2254	ATP-dependent RNA helicase, DEAD-family (deaD)	52.2%
AF0071	ATP-dependent RNA helicase, putative	29.6%
AF1458	ATP-dependent RNA helicase, putative	48.1%
AF2406	ATP-dependent RNA helicase, putative	35.2%
AF1149	large helicase-related protein (lhr-1)	34.5%
AF2177	large helicase-related protein (lhr-2), authentic frameshift	56.0%
AF1220	peptide chain release factor eRF, subunit 1	51.2%
AF2245	SKI2-family helicase, authentic frameshift	45.7%
AF0937	translation elongation factor EF-1, subunit alpha (tuf)	74.4%
AF0574	translation elongation factor EF-1, subunit beta	31.3%
AF1894	translation elongation factor EF-2 (fus)	62.5%
AF0777	translation initiation factor eIF-1A (eif1A)	57.5%
AF0627	translation initiation factor eIF-2, subunit alpha (eif2A)	51.1%
AF2326	translation initiation factor eIF-2, subunit beta, putative	45.5%
AF0592	translation initiation factor eIF-2, subunit gamma (eif2G)	64.4%
AF0370	translation initiation factor eIF-2B, subunit delta (eif2BD)	53.3%
AF2037	translation initiation factor eIF-2B, subunit delta (eif2BD)	57.9%
AF0645	translation initiation factor eIF-5A (eif5A)	50.4%
AF0768	translation initiation factor IF-2 (infB)	52.2%

TRANSPORT AND BINDING PROTEINS

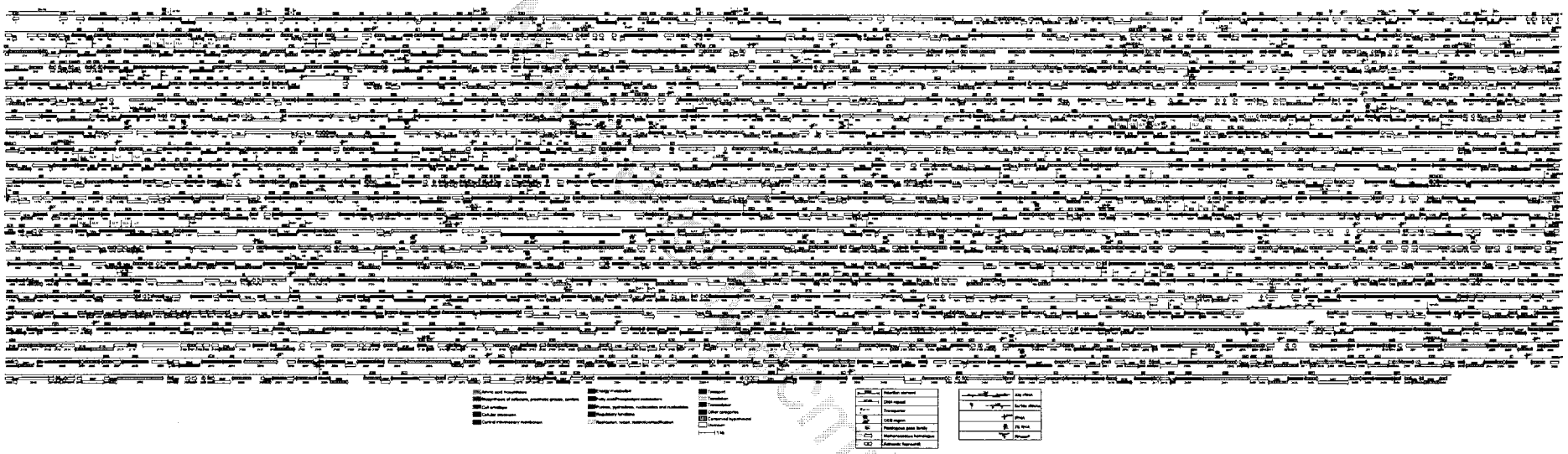
General		
AF0393	ABC transporter, ATP-binding protein	34.5%
AF0984	ABC transporter, ATP-binding protein	35.2%
AF1006	ABC transporter, ATP-binding protein	35.1%
AF1018	ABC transporter, ATP-binding protein	57.7%
AF1021	ABC transporter, ATP-binding protein	37.8%
AF1136	ABC transporter, ATP-binding protein	39.3%
AF1139	ABC transporter, ATP-binding protein	38.2%
AF1300	ABC transporter, ATP-binding protein	34.1%
AF1469	ABC transporter, ATP-binding protein	43.5%
AF1819	ABC transporter, ATP-binding protein	51.1%
AF1982	ABC transporter, ATP-binding protein	41.3%
AF2364	ABC transporter, ATP-binding protein	53.5%
AF1005	ABC transporter, ATP-binding protein, putative	28.7%
AF1064	ABC transporter, ATP-binding protein, putative	36.0%
AF1983	ABC transporter, periplasmic binding protein	25.4%
AF1981	ABC transporter, permease protein	29.9%
AF1995	sodium- and chloride-dependent transporter	52.5%
Amino acids, peptides and amines		
AF1766	amino-acid ABC transporter, periplasmic binding protein/protein kinase	27.4%
AF0222	branched-chain amino acid ABC transporter, ATP-binding protein (braF-1)	42.7%
AF0822	branched-chain amino acid ABC transporter, ATP-binding protein (braF-2)	44.7%
AF0959	branched-chain amino acid ABC transporter, ATP-binding protein (braF-3)	37.6%
AF1390	branched-chain amino acid ABC transporter, ATP-binding protein (braF-4)	59.7%
AF0221	branched-chain amino acid ABC transporter, ATP-binding protein (braG-1)	48.2%
AF0823	branched-chain amino acid ABC transporter, ATP-binding protein (braG-2)	42.9%
AF0958	branched-chain amino acid ABC transporter, ATP-binding protein (braG-3)	34.1%
AF1389	branched-chain amino acid ABC transporter, ATP-binding protein (braG-4)	64.6%
AF0223	branched-chain amino acid ABC transporter, periplasmic binding protein (braC-1)	34.3%
AF0827	branched-chain amino acid ABC transporter, periplasmic binding protein (braC-2)	26.8%
AF0962	branched-chain amino acid ABC transporter, periplasmic binding protein (braC-3)	25.6%
AF1391	branched-chain amino acid ABC transporter, periplasmic binding protein (braC-4)	50.1%
AF0224	branched-chain amino acid ABC transporter, permease protein (braD-1)	25.4%
AF0825	branched-chain amino acid ABC transporter, permease protein (braD-2)	30.8%
AF0961	branched-chain amino acid ABC transporter, permease protein (braD-3)	23.9%
AF1392	branched-chain amino acid ABC transporter, permease protein (braD-4)	65.4%
AF0225	branched-chain amino acid ABC transporter, permease protein (braE-1)	28.7%
AF0824	branched-chain amino acid ABC transporter, permease protein (braE-2)	31.3%
AF0960	branched-chain amino acid ABC transporter, permease protein (braE-3)	30.1%
AF1393	branched-chain amino acid ABC transporter, permease protein (braE-4)	60.5%
AF1612	cationic amino acid transporter (cat-1)	29.5%
AF1774	cationic amino acid transporter (cat-2)	38.0%
AF1770	dipeptide ABC transporter, ATP-binding protein (dppD)	47.8%
AF1771	dipeptide ABC transporter, ATP-binding protein (dppF)	43.1%
AF1767	dipeptide ABC transporter, dipeptide-binding protein (dppA)	33.1%
AF1768	dipeptide ABC transporter, permease protein (dppB)	39.3%
AF1769	dipeptide ABC transporter, permease protein (dppC)	40.8%
AF0680	glutamine ABC transporter, ATP-binding protein (glnQ)	63.8%
AF0231	glutamine ABC transporter, periplasmic glutamine-binding protein (glnH)	38.0%
AF0232	glutamine ABC transporter, permease protein (glnP)	39.3%
AF0981	osmoprotection protein (proV)	39.0%
AF0979	osmoprotection protein (proW-1)	32.8%
AF0980	osmoprotection protein (proW-2)	36.8%
AF0982	osmoprotection protein (proX)	28.7%
AF0015	proline permease (putP-1)	26.2%
AF0989	proline permease (putP-2)	27.4%
AF1222	proline permease (putP-3)	27.0%
AF1808	spermidine/putrescine ABC transporter, ATP-binding protein (potA)	50.2%
AF1606	spermidine/putrescine ABC transporter, periplasmic spermidine/putrescine-binding protein (potD), authentic frameshift	31.0%
AF1607	spermidine/putrescine ABC transporter, permease protein (potB)	38.0%
AF1606	spermidine/putrescine ABC transporter, permease protein (potC)	38.7%
Anions		
AF2308	arsenite transport protein (arsB)	27.3%
AF1415	chloride channel, putative	27.3%
AF0025	cyanate transport protein (cynX)	24.5%
AF0087	nitrate ABC transporter, ATP-binding protein (nrtC-1)	47.4%
AF0638	nitrate ABC transporter, ATP-binding protein (nrtC-2)	55.5%
AF0640	nitrate ABC transporter, ATP-binding protein, putative	32.5%
AF0086	nitrate ABC transporter, permease protein (nrtB-1)	35.4%
AF0639	nitrate ABC transporter, permease protein (nrtB-2)	37.4%
AF1359	phosphate ABC transporter, ATP-binding protein (pstB)	66.0%
AF1356	phosphate ABC transporter, periplasmic phosphate-binding protein (phoX)	25.1%
AF1358	phosphate ABC transporter, permease protein (pstA)	34.1%
AF1357	phosphate ABC transporter, permease protein (pstC)	33.7%
AF1360	phosphate ABC transporter, regulatory protein (phoU)	26.9%
AF0791	phosphate permease, putative	31.1%
AF1798	phosphate permease, putative	52.9%
AF0092	sulfate ABC transporter, ATP-binding protein (cysA)	54.2%
AF0093	sulfate ABC transporter, permease protein (cysT)	44.1%
Carbohydrates, organic alcohols, and acids		
AF0347	C4-dicarboxylate transporter (mae1)	24.5%
AF1426	glycerol uptake facilitator, MIP channel (glpF)	36.2%
AF0013	hexuronate transporter (exuT)	25.1%
AF0806	L-lactate permease (lctP)	31.7%
AF0008	oxalate/formate antiporter (oxlT-1)	25.7%
AF0367	oxalate/formate antiporter (oxlT-2)	33.2%
AF1069	pantothenate permease (panF-1)	28.9%
AF1205	pantothenate permease (panF-2)	24.8%
AF0237	pantothenate permease (panF-3)	25.1%
AF0041	polysaccharide ABC transporter, ATP-binding protein (rfbB-1)	42.5%
AF0290	polysaccharide ABC transporter, ATP-binding protein (rfbB-2)	43.9%
AF0042	polysaccharide ABC transporter, permease protein (rfbA-1)	27.5%
AF0289	polysaccharide ABC transporter, permease protein (rfbA-2)	28.5%
AF0887	ribose ABC transporter, ATP-binding protein (rbsA-1)	33.3%
AF1170	ribose ABC transporter, ATP-binding protein (rbsA-2)	27.9%
AF0888	ribose ABC transporter, permease protein (rbsC-1)	24.1%
AF0889	ribose ABC transporter, permease protein (rbsC-2)	31.2%
AF2014	sugar transporter, putative	26.0%
Cations		
AF0977	ammonium transporter (amt-1)	44.3%
AF1746	ammonium transporter (amt-2)	49.0%
AF1749	ammonium transporter (amt-3)	41.5%
AF0473	cation-transporting ATPase, P-type (pacS)	44.0%
AF0152	copper-transporting ATPase, P-type (copB)	44.5%
AF0246	iron (II) transporter (feoB-1)	33.3%
AF2394	iron (II) transporter (feoB-2)	48.0%
AF0661	iron (II) transporter (feoB-3), authentic frameshift	29.4%
AF0430	iron (III) ABC transporter, ATP-binding protein (hemV-1)	50.4%
AF0432	iron (III) ABC transporter, ATP-binding protein (hemV-2)	58.7%
AF1401	iron (III) ABC transporter, ATP-binding protein (hemV-3)	35.2%
AF1397	iron (III) ABC transporter, periplasmic hemin-binding protein (hemT), authentic frameshift	28.2%
AF0431	iron (III) ABC transporter, permease protein (hemU-1)	36.2%
AF1402	iron (III) ABC transporter, permease protein (hemU-2)	35.2%
AF0786	magnesium and cobalt transporter (corA)	40.1%
AF0346	mercuric transport protein periplasmic component (merP)	35.2%
AF0217	Na+/H+ antiporter (napA-1)	28.2%
AF1245	Na+/H+ antiporter (napA-2)	28.4%
AF0846	Na+/H+ antiporter (nhe2)	33.1%
AF0715	potassium channel, putative	39.5%
AF1673	potassium channel, putative	38.3%
AF2197	potassium channel, putative	24.6%
AF0218	TRK potassium uptake system protein (trkA-1)	30.2%
AF0838	TRK potassium uptake system protein (trkA-2)	42.9%
AF0839	TRK potassium uptake system protein (trkH)	39.8%
Other		
AF0834	ferritin, putative	39.8%
AF1980	heme exporter protein C (helC)	29.0%
AF1144	multidrug resistance protein	29.2%
AF1325	multidrug resistance protein	29.9%
AF2258	multidrug resistance protein	31.3%

OTHER CATEGORIES

Adaptations and atypical conditions		
AF0508	ethylene-inducible protein	74.5%
AF0235	heat shock protein (htpX)	32.9%
AF0942	surE stationary-phase survival protein (surE)	50.2%
AF1998	virulence associated protein C (vapC-1)	50.0%
AF1690	virulence associated protein C (vapC-2)	30.0%
Drug and analog sensitivity		
AF1884	daunorubicin resistance ATP-binding protein (drrA)	47.1%
AF1883	daunorubicin resistance membrane protein (drrB)	27.0%
AF0487	penicillin G acylase	31.7%
AF1214	phenylacrylic acid decarboxylase (pad1)	43.2%
AF2194	rRNA (adenine-N6)-methyltransferase, putative	29.2%
AF1696	small multidrug export protein (qacE)	39.0%
Transposon-related functions		
AF0120	insertion sequence ISH S1, authentic frameshift	34.5%
AF0193	ISA0963-1, putative transposase, authentic frameshift	34.3%
AF0309	ISA0963-2, putative transposase	33.5%
AF1310	ISA0963-3, putative transposase	33.5%
AF1383	ISA0963-4, putative transposase	33.5%
AF1410	ISA0963-5, putative transposase	33.5%
AF1705	ISA0963-6, putative transposase	33.5%
AF1836	ISA0963-7, putative transposase, authentic frameshift	20.0%
AF0678	ISA1083-1, ISORF2	33.6%
AF0679	ISA1083-1, putative transposase	37.2%
AF1351	ISA1083-2, ISORF2	30.8%
AF1352	ISA1083-2, putative transposase	31.5%
AF2140	ISA1083-3, ISORF2	30.8%
AF2139	ISA1083-3, putative transposase	31.5%
AF0278	ISA1214-1, ISORF2	27.7%
AF0279	ISA1214-1, putative transposase	33.3%
AF0305	ISA1214-2, ISORF2	27.7%
AF0306	ISA1214-2, putative transposase	33.3%
AF0641	ISA1214-3, ISORF2	26.5%
AF0642	ISA1214-3, putative transposase	33.3%
AF0857	ISA1214-4, ISORF2	27.7%
AF0858	ISA1214-4, putative transposase	33.3%
AF2091	ISA1214-5, ISORF2	26.5%
AF2092	ISA1214-5, putative transposase	33.3%
AF2223	ISA1214-6, ISORF2	26.5%
AF2222	ISA1214-6, putative transposase	25.6%
AF0138	transposase IS240-A	43.3%
AF0895	transposase IS240-A	46.2%
AF2390	transposase, authentic frameshift	24.0%
AF0137	transposase, putative	29.6%
AF1628	transposase, putative	32.8%

UNKNOWN

AF0477	AAA superfamily ATPase	35.0%
AF0513	allene oxide synthase, putative	39.5%
AF0478	ATP-binding protein PhnP (phnP)	30.9%
AF1775	atrazine chlorohydrolase, putative	34.4%
AF0973	bile acid-inducible operon protein F (baiF-1)	30.8%
AF0974	bile acid-inducible operon protein F (baiF-2)	29.9%
AF1315	bile acid-inducible operon protein F (baiF-3)	31.3%
AF2063	c-myc binding protein, putative	21.7%
AF1992	calcium-binding protein, putative	31.2%
AF2287	carotenoid biosynthetic gene ERWCRTS, putative	49.4%
AF0512	chloroplast inner envelope membrane protein	42.5%
AF2251	competence-damage protein, putative	28.0%
AF0090	dehydrase	34.1%
AF1498	dehydrase, putative	29.4%
AF1518	DNA/pantothenate metabolism flavoprotein, putative	51.4%
AF0039	dolichol-P-glucose synthetase, putative	33.7%
AF0328	dolichol-P-glucose synthetase, putative	39.0%
AF0581	dolichol-P-glucose synthetase, putative	27.5%
AF0569	DR-beta chain MHC class II	37.7%
AF0383	endonuclease III, putative	47.1%
AF1150	erpK protein, putative	54.9%
AF2372	extragenic suppressor (suhB)	37.0%
AF1418	glycerol-3-phosphate cytidyltransferase (taqD)	56.6%
AF0744	GTP-binding protein	33.4%
AF1181	GTP-binding protein	36.3%
AF1364	GTP-binding protein	57.5%
AF2146	GTP-binding protein	65.9%
AF0428	GTP-binding protein, GTP1/OBG-family	43.9%
AF2237	HAM1 protein	31.4%
AF2211	HIT family protein (hit)	29.6%
AF0216	L-isoaspartyl protein carboxyl methyltransferase PimT, putative	35.5%
AF2313	maoC protein (maoC)	43.0%
AF0429	methyltransferase	43.8%
AF0186	nifS protein, class-V aminotransferase (nifS-1)	46.1%
AF0564	nifS protein, class-V aminotransferase (nifS-2)	46.1%
AF0186	nifU protein (nifU-1)	55.6%
AF0565	nifU protein (nifU-2)	55.6%
AF0632	nifU protein (nifU-3)	47.4%
AF1781	nodulation protein NfeD (nfeD)	33.4%
AF2269	nucleotide-binding protein	48.7%
AF2382	nucleotide-binding protein	48.1%
AF0374	p-nitrophenyl phosphatase (pho2)	31.7%
AF1978	periplasmic divalent cation tolerance protein (cutA)	31.3%
AF1652	prepro-subtilisin sendai, putative	35.6%
AF2021	rod shape-determining protein (mreB)	26.6%
AF1778	stage V sporulation protein (spoVG)	43.9%
AF1970	TPR domain-containing protein	29.0%
AF2202	tryptophan-specific permease, putative	25.2%
AF0815	vtpI-therm, putative	42.1%
AF1679	vtpI-therm, putative	46.1%



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The complete genome sequence of the hyperthermophilic, sulphate-reducing archaeon *Archaeoglobus fulgidus*

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Archaeoglobus fulgidus **is the first sulphur-metabolizing organism to have its genome sequence determined. Its genome of 2,178,400 base pairs contains 2,436 open reading frames (ORFs). The information processing systems and the biosynthetic pathways for essential components (nucleotides, amino acids and cofactors) have extensive correlation with their counterparts in the archaeon *Methanococcus jannaschii*. The genomes of these two Archaea indicate dramatic differences in the way these organisms sense their environment, perform regulatory and transport functions, and gain energy. In contrast to *M. jannaschii*, *A. fulgidus* has fewer restriction-modification systems, and none of its genes appears to contain inteins. A quarter (651 ORFs) of the *A. fulgidus* genome encodes functionally uncharacterized yet conserved proteins, two-thirds of which are shared with *M. jannaschii* (428 ORFs). Another quarter of the genome encodes new proteins indicating substantial archaeal gene diversity.**

Biological sulphate reduction is part of the global sulphur cycle, ubiquitous in the earth's anaerobic environments, and is essential to the basal workings of the biosphere. Growth by sulphate reduction is restricted to relatively few groups of prokaryotes; all but one of these are Eubacteria, the exception being the archaeal sulphate reducers in the Archaeoglobales[1,2]. These organisms are unique in that they are unrelated to other sulphate reducers, and because they grow at extremely high temperatures[3]. The known Archaeoglobales are strict anaerobes, most of which are hyperthermophilic marine sulphate reducers found in hydrothermal environments[2,4] and in subsurface oil fields[5]. High-temperature sulphate reduction by *Archaeoglobus* species contributes to deep subsurface oil-well 'souring' by producing iron sulphide, which causes corrosion of iron and steel in oil- and gas-processing systems[5].

Archaeoglobus fulgidus VC-16 (refs 2, 4) is the type strain of the Archaeoglobales. Cells are irregular spheres with a glycoprotein envelope and monopolar flagella. Growth occurs between 60 and 95 °C, with optimum growth at 83 °C and a minimum division time of 4 h. The organism grows organoheterotrophically using a variety of carbon and energy sources, but can grow lithoautotrophically on hydrogen, thiosulphate and carbon dioxide[6]. We sequenced the genome of *A. fulgidus* strain VC-16 as an example of a sulphur-metabolizing organism and to gain further insight into the Archaea[7,8] through genomic comparison with *Methanococcus jannaschii*[9].

General features of the genome

The genome of *A. fulgidus* consists of a single, circular chromosome of 2,178,400 base pairs (bp) with an average of 48.5% G+C content (Fig. 1). There are three regions with low G+C content (<39%), two rich in genes encoding enzymes for lipopolysaccharide (LPS) biosynthesis, and two regions of high G+C content (>53%), containing genes for large ribosomal RNAs, proteins involved in haem biosynthesis (*hemAB*), and several transporters (Table 1). Because the origins of replication in Archaea are not characterized, we arbitrarily designated base pair one within a presumed non-coding region upstream of one of three areas containing multiple short repeat elements.

Open reading frames. Two independent coding analysis programs and BLASTX[10] searches (see Methods) predicted 2,436 ORFs (Figs 1, 2, Tables 1, 2) covering 92.2% of the genome. The average size of the *A. fulgidus* ORFs is 822 bp, similar to that of *M. jannaschii* (856 bp), but smaller than that in the completely sequenced eubacterial genomes (949 bp). All ORFs were searched against a non-redundant protein database, resulting in 1,797 putative identifications that were assigned biological roles within a classification system adapted from ref. 11. Predicted start codons are 76% ATG, 22% GTG and 2% TTG. Unlike *M. jannaschii*, where 18 inteins were found in coding regions, no inteins were identified in *A. fulgidus*. Compared with *M. jannaschii*, *A. fulgidus* contains a large number of gene duplications, contributing to its larger genome size. The average protein relative molecular mass (M_r) in *A. fulgidus* is 29,753, ranging from 1,939 to 266,571, similar to that observed in other prokaryotes. The isoelectric point (pI) of predicted proteins among sequenced prokaryotes exhibits a bimodal distribution with peaks at pIs of approximately 5.5 and 10.5. The exceptions to this are *Mycoplasma genitalium* in which the distribution is skewed towards high pI

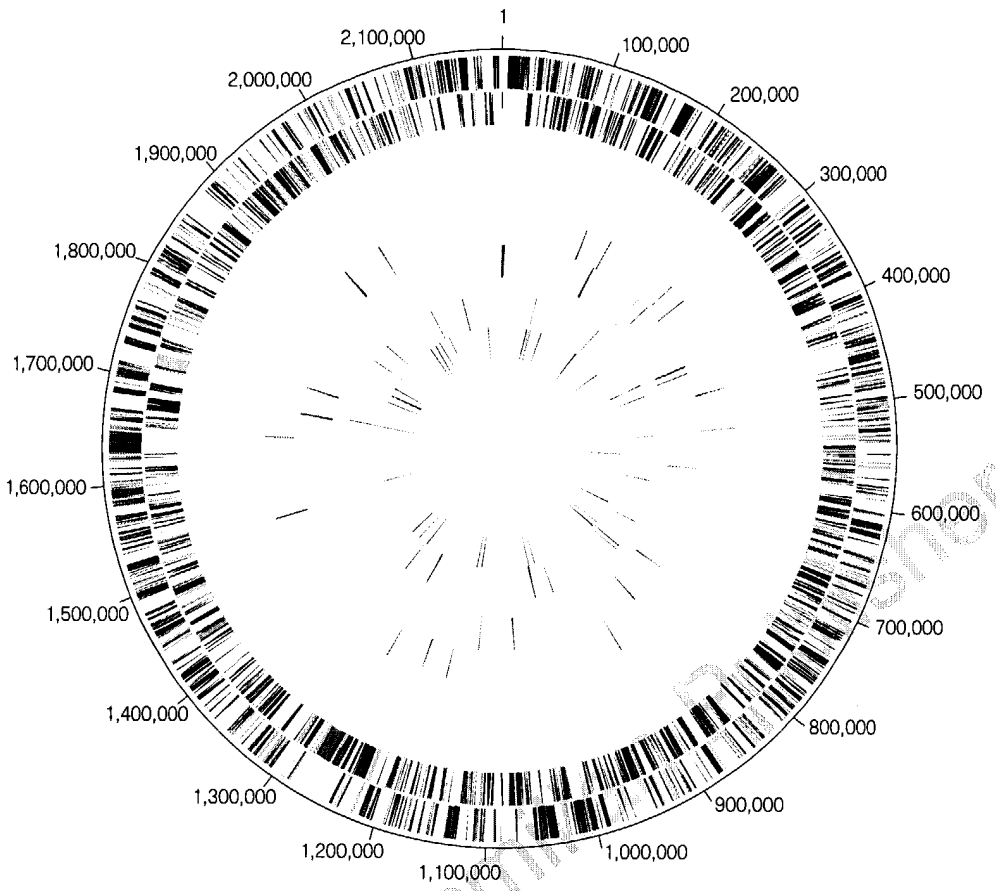

Figure 1 Circular representation of the *A. fulgidus* genome. The outer circle shows predicted protein-coding regions on the plus strand classified by function according to the colour code in Fig. 2 (except for unknowns and hypotheticals, which are in black). Second circle shows predicted protein-coding regions on the minus strand. Third and fourth circles show IS elements (red) and other repeats (green) on the plus and minus strand. Fifth and sixth circles show tRNAs (blue), rRNAs (red) and sRNAs (green) on the plus and minus strand, respectively.

Table 1 Genome features

General		
Chromosome size:	2,178,400 bp	
Protein coding regions:	92.2%	
Stable RNAs:	0.4%	
Predicted protein coding sequences:	2,436 (1.1 per kb)	
Identified by database match:	1,797	
putative function assigned:	1,096	
homologues of *M. jannaschii* ORFs:	916	
conserved hypothetical proteins:	651	
No database match:	639	
Members of 242 paralogous families:	719	
Members of 158 families with known functions:	475	
Stable RNAs	*Coordinates*	
16S rRNA:	1,790,478–1,788,987	
23S rRNA	1,788,751–1,785,820	
5S rRNA:	81,144–81,021	
7S RNA:	798,067–798,376	
RNase P:	86,281–86,032	
46 species of tRNA:	no significant clusters	
tRNAs with 15–62 bp introns:	Asp^{GUC}, Glu^{UUC}, Leu^{CAA}, Trp^{CCA}, Tyr^{GUA}	
Distinct G+C content regions	*Coordinates*	
HGC-1, >53% G+C	1,786,000–1,797,000	
HGC-2, >53% G+C	2,158,000–2,159,000	
LGC-1, <39% G+C	281,000–284,000	
LGC-2, <39% G+C	544,000–550,000	
LGC-3, <39% G+C	1,175,000–1,177,000	
Short, non-coding repeats	*Coordinates*	
SR-1A, CTTTCAATCCCATTTTGGTCTGATTTCAAC	147–4,213	
SR-1B, CTTTCAATCCCATTTTGGTCTGATTTCAAC	398,368–401,590	
SR-2, CTTTCAATCTCCATTTTCAGGGCCTCCCTTTCTTA	1,690,930–1,694,104	
Long, coding repeats	*Length*	*Copy number*
LR-01 NADH-flavin oxidoreductase	1,886 bp	2 copies
LR-02 NifS, NifU + ORF	1,549 bp	2 copies
LR-03 ISA1214 putative transposase + ISORF2	1,214 bp	6 copies
LR-04 ISA1083 putative transposase + ISORF2	1,083 bp	3 copies
LR-05 type II secretion system protein	1,014 bp	4 copies
LR-06 ISA0963 putative transposase	963 bp	7 copies
LR-07 homologue of MJ0794	836 bp	3 copies
LR-08 conserved hypothetical protein	696 bp	2 copies
LR-09 conserved hypothetical protein	628 bp	2 copies

(median, 9.8) and *A. fulgidus* where the skew is toward low pI (median, 6.3).

Multigene families. In *A. fulgidus* 719 genes (30% of the total) belong to 242 families with two or more members (Table 1). Of these families, 157 contained genes with biological roles. Most of these families contain genes assigned to the 'energy metabolism', 'transport and binding proteins', and 'fatty acid and phospholipid metabolism' categories (Table 2). The superfamily of ATP-binding subunits of ABC transporters is the largest, containing 40 members. The importance of catabolic degradation and signal recognition systems is reflected by the presence of two large superfamilies: acyl-CoA ligases and signal-transducing histidine kinases. *A. fulgidus* does not contain a homologue of the large 16-member family found in *M. jannaschii*[9].

Repetitive elements. Three regions of the *A. fulgidus* genome contain short (<40 bp) direct repeats (Table 1). Two regions (SR-1A and SR-1B) contain 48 and 60 copies, respectively, of an identical 30-bp repeat interspersed with unique sequences averaging 40 bp. The third region (SR-2) contains 42 copies of a 37-bp repeat similar in sequence to the SR-1 repeat and interspersed with unique sequence averaging 41 bp. These repeated sequences are similar to the short repeated sequences found in *M. jannaschii*.

Nine classes of long (>500 bp) repeated sequences with ≥95% sequence identity were found (LR1-LR9; Table 1). LR-3 is a novel element with 14-bp inverted repeats and two genes, one of which has weak similarity to a transposase from *Halobacterium salinarium*. One copy of LR-3 interrupts AF2090, a homologue of a large *M. jannaschii* gene encoding a protein of unknown function. LR-4 and LR-6 encode putative transposases not identified in *M. jannaschii* that may represent IS elements. The remaining LR elements are not similar to known IS elements.

Central intermediary and energy metabolism

Sulphur oxide reduction may be the dominant respiratory process in anaerobic marine and freshwater environments, and is an important aspect of the sulphur cycle in anaerobic ecosystems[12]. In this pathway, sulphate (SO_4^{2-}) is first activated to adenylylsulphate (adenosine-5′-phosphosulphate; APS), then reduced to sulphite and subsequently to sulphide[1,13] (Fig. 3). The most important enzyme in dissimilatory sulphate reduction, adenylylsulphate reductase, reduces the activated sulphate to sulphite, releasing AMP. In *A. fulgidus*, the APS reductase has a high degree of similarity and identical physiological properties to APS reductases in sulphate-reducing delta proteobacteria[14]. A desulphoviridin-type sulphite reductase then adds six electrons to sulphite to produce sulphide. As in the Eubacteria, three sulphite-reductase genes, *dsrABD*, constitute an operon. The genes for adenylylsulphate reductase and sulphate adenylyltransferase reside in a separate operon. In *A. fulgidus*, sulphate can be replaced as an electron acceptor by both thiosulphate ($S_2O_3^{2-}$) and sulphite (SO_3^{2-}), but not by elemental sulphur.

A. fulgidus VC-16 has been shown to use lactate, pyruvate, methanol, ethanol, 1-propanol and formate as carbon and energy sources[2]. Glucose has been described as a carbon source[1], but neither an uptake-transporter nor a catabolic pathway could be identified. Although it has been reported that *A. fulgidus* is incapable of growth on acetate[6], multiple genes for acetyl-CoA synthetase (which converts acetate to acetyl-CoA) were found. The organism may degrade a variety of hydrocarbons and organic acids because of the presence of 57 β-oxidation enzymes, at least one lipase, and a minimum of five types of ferredoxin-dependent oxidoreductases (Fig. 3). The predicted β-oxidation system is similar to those in Eubacteria and mitochondria, and has not previously been described in the Archaea. *Escherichia coli* requires both the *fadD* and *fadL* gene products to import long-chain fatty acids across the cell envelope into the cytosol[15]. *A. fulgidus* has 14 acyl-CoA ligases related to FadD, but as expected given that it has no outer membrane, no FadL. In *E. coli*, FadB has several metabolic functions, but in *A. fulgidus* these functions seem to be distributed among separate enzymes. For example, AF0435 encodes an orthologue of enoyl-CoA hydratase and resembles the amino-terminal domain of FadB. This gene is immediately upstream of a gene encoding an orthologue of 3-hydroxyacyl-CoA dehydrogenase that resembles the carboxy-terminal domain of FadB.

Acetyl-CoA is degraded by *A. fulgidus* through a C_1-pathway, not by the citric acid cycle or glyoxylate bypass[6,16,17]. This degradation is catalysed through the carbon monoxide dehydrogenase (CODH) pathway that consists of a five-subunit acetyl-CoA decarboxylase/synthase complex (ACDS) and five enzymes that are typically involved in methanogenesis[18]. In *A. fulgidus*, however, reverse methanogenesis occurs, resulting in CO_2 production. All of the enzymes and cofactors of methanogenesis from formylmethanofuran to N^5-methyltetrahydromethanopterin are used, but the absence of methyl-CoM reductase eliminates the possibility of methane production by conventional pathways. Production of trace amounts of methane (<0.1 μmol ml^{-1})[19] is probably a result of the reduction of N^5-methyltetrahydromethanopterin to methane and tetrahydromethanopterin by carbon monoxide (CO) dehydrogenase.

A. fulgidus also contains genes suggesting it has a second CO dehydrogenase system, homologous to that which enables *Rhodospirillum rubrum* to grow without light using CO as its sole energy source. Genes were detected for the nickel-containing CO dehydrogenase (CooS), an iron–sulphur redox protein, and a protein associated with the incorporation of nickel in CooS. These represent elements of a system that could catalyse the conversion of CO and H_2O to CO_2 and H_2.

In contrast to *M. jannaschii*, *A. fulgidus* contains genes representing multiple catabolic pathways. Systems include CoA-SH-dependent ferredoxin oxidoreductases specific for pyruvate, 2-ketoisovalerate, 2-ketoglutarate and indolepyruvate, as well as a 2-oxoacid with little substrate specificity[20,21]. Four genes with similarity to the tungsten-containing aldehyde ferredoxin oxidoreductase were also found[22].

Biochemical pathways characteristic of eubacterial metabolism, including the pentose-phosphate pathway, the Entner–Doudoroff pathway, glycolysis and gluconeogenesis, are either completely absent or only partly represented (Fig. 3). *A. fulgidus* does not have typical eubacterial polysaccharide biosynthesis machinery, yet it has been shown to produce a protein and carbohydrate-containing biofilm[23]. Nitrogen is obtained by importing inorganic molecules or degrading amino acids (Fig. 3); neither a glutamate dehydrogenase nor a relevant *fix* or *nif* gene is present.

The $F_{420}H_2$:quinone oxidoreductase complex[24] is recognized as

Figure 2 Linear representation of the *A. fulgidus* genome illustrating the location of each predicted protein-coding region, RNA gene, and repeat element in the genome. Symbols for the transporters are as follows: AsO, arsenite; COH, sugar; P_i, phosphate; aa2, dipeptide; NH_4^+, ammonium; a/o, arginine/lysine/ornithine; s/p, spermidine/putrescine; glyc, glycerol; Cl^-, chloride; Fe^{2+}, iron(II); Fe^{3+}, iron(III); I, L, V, branched-chain amino acids; P, proline; pan, pantothenate; rib, ribose; lac, lactate; Mg^{2+}/Co^{2+}, magnesium and cobalt; gln, glutamine; NO^{3-}, nitrate; ox/for, oxalate/formate; maln, malonic acid; Hg^{2+}, mercury; phs, polysaccharide; SO_4^{2-}, sulphate; OCN^-, cyanate; hex, hexuronate; phs, polysialic acid; K^+, potassium channel; H^+/Na^+, sodium/proton antiporter; Na^+/Cl^-, sodium- and chloride-dependent transporter; P/G, osmoprotection protein; Cu^{2+}, copper-transporting ATPase; +?, cation-transporting ATPase; ?, ABC-transporter without known function. Triplets associated with tRNAs represent the anticodon sequence. Numbers associated with GES represent the number of membrane-spanning domains (MSDs) according to Goldman, Engelman and Steiz scale as determined by TopPred[39]. Genes whose identification is based on genes in *M. jannaschii* are indicated by circles. Of the 236 proteins containing at least one MSD, 124 of these had two or more MSDs.

the main generator of proton-motive force. However, our analysis indicates the presence of heterodisulphide reductase and several molybdopterin-binding oxidoreductases, with polysulphide, nitrate, dimethyl sulphoxide, and thiosulphate as potential substrates, which might contribute to energizing the cell membrane. *A. fulgidus* contains a large number of flavoproteins, iron–sulphur proteins and iron-binding proteins that contribute to the general intracellular flow of electrons (Fig. 3). Detoxification enzymes include a peroxidase/catalase, an alkyl-hydroperoxide reductase, arsenate reductase, and eight NADH oxidases, presumably catalysing the

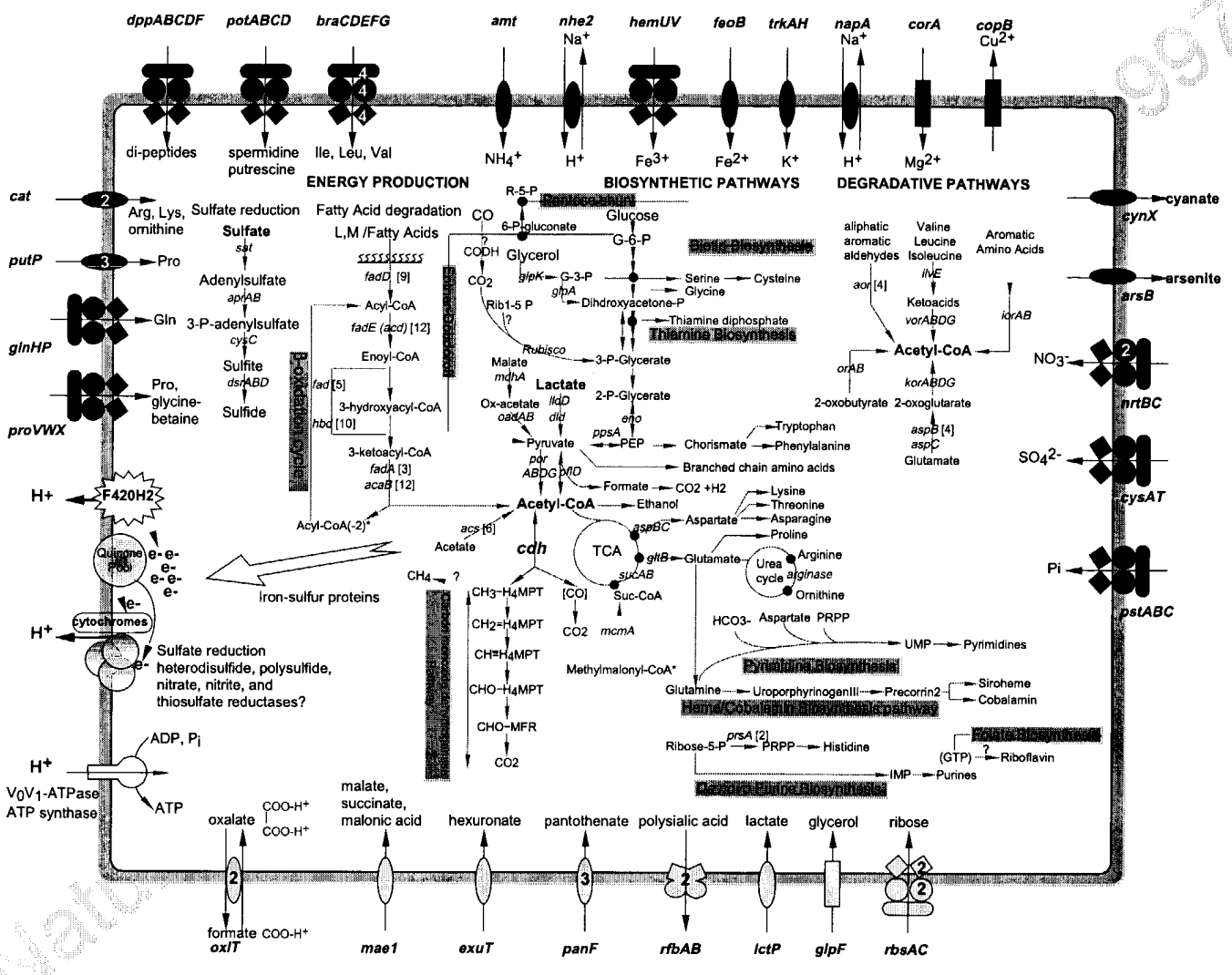

Figure 3 An integrated view of metabolism and solute transport in *A. fulgidus*. Biochemical pathways for energy production, biosynthesis of organic compounds, and degradation of amino acids, aldehydes and acids are shown with the central components of *A. fulgidus* metabolism, sulphate, lactate and acetyl-CoA highlighted. Pathways or steps for which no enzymes were identified are represented by a red arrow. A question mark is attached to pathways that could not be completely elucidated. Macromolecular biosynthesis of RNA, DNA and ether lipids have been omitted. Membrane-associated reactions that establish the proton-motive force (PMF) and generate ATP (electron transport chain and V_1V_0-ATPase) are linked to cytosolic pathways for energy production. The oxalate-formate antiporters (*oxlT*) may also contribute to the PMF by mediating electrogenic anion exchange. Each gene product with a predicted function in ion or solute transport is illustrated. Proteins are grouped by substrate specificity with transporters for cations (green), anions (red), carbohydrates/organic alcohols/acids (yellow), and amino acids/peptides/amines (blue) depicted. Ion-coupled permeases are represented by ovals (*mae1*, *exuT*, *panF*, *lctP*, *arsB*, *cynX*, *napA/nhe2*, *amt*, *feoB*, *trkAH*, *cat* and *putP* encode transporters for malate, hexuronate, pantothenate, lactate, arsenite, cyanate, sodium, ammonium, iron (II), potassium, arginine/lysine and proline, respectively). ATP-binding cassette (ABC) transport systems are shown as composite figures of ovals, diamonds and circles (*proVWX*, *glnHPQ*, *dppABCDF*, *potABCD*, *braCDEFG*, *hemUV*, *nrtBC*, *cysAT*, *pstABC*, *rbsAC*, *rfbAB* correspond to gene products for proline, glutamine, dipeptide, spermidine/putrescine, branch-chain amino acids, iron (III), nitrate, sulphate, phosphate, ribose and polysialic acid transport, respectively). All other porters drawn as rectangles (*glpF*, glycerol uptake facilitator; *copB*, copper transporting ATPase; *corA*, magnesium and cobalt transporter). Export and import of solutes is designated by arrows. The number of paralogous genes encoding each protein is indicated in brackets for cytoplasmic enzymes, or within the figure for transporters. Abbreviations: *acs*, acetyl-CoA synthetase; *aor*, aldehyde ferredoxin oxidoreductase; *aprAB*, adenylylsulphate reductase; *aspBC*, aspartate aminotransferase; *cdh*, acetyl-CoA decarbonylase/synthase complex; *cysC*, adenylylsulphate 3-phosphotransferase; *dld*, D-lactate dehydrogenase; *dsrABD*, sulphite reductase; *eno*, enolase; *fadA/acaB*, 3-ketoacyl-CoA thiolase; *fadD*, long-chain-fatty-acid-CoA ligase; *fad*, enoyl-CoA hydratase; *fadE* (*acd*), acyl-CoA dehydrogenase; *glpA*, glycerol-3-phosphate dehydrogenase; *glpK*, glycerol kinase; *gltB*, glutamate synthase; *hbd*, 3-hydroxyacyl-CoA dehydrogenase; *ilvE*, branched-chain amino-acid aminotransferase; *iorAB*, indolepyruvate ferredoxin oxidoreductase; *korABDG*, 2-ketoglutarate ferredoxin oxidoreductase; *lldD*, L-lactate dehydrogenase; *mcmA*, methylmalonyl-CoA mutase; *mdhA*, L-malate dehydrogenase; *oadAB*, oxaloacetate decarboxylase; *orAB*, 2-oxoacid ferredoxin oxidoreductase; *pflD*, pyruvate formate lysase 2; *porABDG*, pyruvate ferredoxin oxidoreductase; *ppsA*, phosphoenolpyruvate synthase; *prsA*, ribose-phosphate pyrophosphokinase; *sucAB*, 2-ketoglutarate dehydrogenase; *sat*, sulphate adenylyltransferase; TCA, tricarboxylic acid cycle; *vorABDG*, 2-ketoisovalerate ferredoxin oxidoreductase.

four-electron reduction of molecular oxygen to water, with the concurrent regeneration of NAD.

Transporters

A. fulgidus may synthesize several transporters for the import of carbon-containing compounds, probably contributing to its ability to switch from autotrophic to heterotrophic growth[5]. Both *M. jannaschii* and *A. fulgidus* have branched-chain amino-acid ABC transport systems and a transporter for the uptake of arginine and lysine. *A. fulgidus* encodes proteins for dipeptide, spermidine/putrescine, proline/glycine-betaine and glutamine uptake, as well as transporters for sugars and acids, rather like the membrane systems described in eubacterial heterotrophs. These compounds provide the necessary substrates for numerous biosynthetic and degradative pathways (Fig. 3).

Many *A. fulgidus* redox proteins are predicted to require iron. Correspondingly, iron transporters have been identified for the import of both oxidized (Fe^{3+}) and reduced (Fe^{2+}) forms of iron. There are duplications in functional and regulatory genes in both systems. The uptake of Fe^{3+} may depend on haemin or a haemin-like compound because *A. fulgidus* has orthologues to the eubacterial *hem* transport system proteins, HemU and HemV. *A. fulgidus* may also use the regulatory protein Fur to modulate Fe^{3+} transport; this protein is not present in *M. jannaschii*. Fe^{2+} uptake occurs through a modified Feo system containing FeoB. This is the third example of an isolated *feoB* gene: *M. jannaschii* and *Helicobacter pylori* also appear to lack *feoA*, implying that FeoA is not essential for iron transport in these organisms.

A complex suite of proteins regulates ionic homeostasis. Ten distinct transporters facilitate the flux of the physiological ions K^+, Na^+, NH_4^+, Mg^{2+}, Fe^{2+}, Fe^{3+}, NO_3^-, SO_4^{2-} and inorganic phosphate (P_i). Most of these transporters have homologues in *M. jannaschii* and are therefore likely to be critical for nutrient acquisition during autotrophic growth. *A. fulgidus* has additional ion transporters for the elimination of toxic compounds including copper, cyanate and arsenite. As in *M. jannaschii*, the *A. fulgidus* genome contains two paralogous operons of cobalamin biosynthesis-cobalt transporters, *cbiMQO*.

Sensory functions and regulation of gene expression

Consistent with its extensive energy-producing metabolism and versatile system for carbon utilization, *A. fulgidus* has complex sensory and regulatory networks. These networks contain over 55 proteins with presumed regulatory functions, including members of the ArsR, AsnC and Sir2 families, as well as several iron-dependent repressor proteins. There are at least 15 signal-transducing histidine kinases, but only nine response regulators; this difference suggests there is a high degree of cross-talk between kinases and regulators. Only four response regulators appear to be in operons with histidine kinases, including those in the methyl-directed chemotaxis system (Che), which lies adjacent to the flagellar biosynthesis operon. Although rich in regulatory proteins, *A. fulgidus* apparently lacks regulators for response to amino-acid and carbon starvation as well as to DNA damage. Finally, *A. fulgidus* contains a homologue of the mammalian mitochondrial benzodiazepine receptor, which functions as a sensor in signal-transduction pathways[25]. These receptors have been previously identified only in Proteobacteria and Cyanobacteria[25].

Replication, repair and cell division

A. fulgidus possesses two family B DNA polymerases, both related to the catalytic subunit of the eukaryal delta polymerase, as previously observed in the Sulfolobales[26]. It also has a homologue of the proofreading ε subunit of *E. coli* Pol III, not previously observed in the Archaea. The DNA repair system is more extensive than that found in *M. jannaschii*, including a homologue of the eukaryal Rad25, a 3-methyladenine DNA glycosylase, and exodeoxynuclease III. As well as reverse gyrase, topoisomerase I (ref. 9), and topoisomerase VI (ref. 27), the genes for the first archaeal DNA gyrase were identified.

A. fulgidus lacks a recognizable type II restriction-modification system, but contains one type I system. In contrast, two type II and three type I systems were identified in *M. jannaschii*. No homologue of the *M. jannaschii* thermonuclease was identified.

The cell-division machinery is similar to that of *M. jannaschii*, with orthologues of eubacterial *fts* and eukaryal *cdc* genes. However, several *cdc* genes found in *M. jannaschii*, including homologues of *cdc23*, *cdc27*, *cdc47* and *cdc54*, appear to be absent in *A. fulgidus*.

Transcription and translation

A. fulgidus and *M. jannaschii* have transcriptional and translational systems distinct from their eubacterial and eukaryal counterparts. In both, the RNA polymerase contains the large universal subunits and five smaller subunits found in both Archaea and eukaryotes. Transcription initiation is a simplified version of the eukaryotic mechanism[28,29]. However, *A. fulgidus* alone has a homologue of eukaryotic TBP-interacting protein 49 not seen in *M. jannaschii*, but apparently present in *Sulfolobus solfactaricus*.

Translation in *A. fulgidus* parallels *M. jannaschii* with a few exceptions. The organism has only one rRNA operon with an Ala-tRNA gene in the spacer and lacks a contiguous 5S rRNA gene. Genes for 46 tRNAs were identified, five of which contain introns in the anticodon region that are presumably removed by the intron excision enzyme EndA. The gene for selenocysteine tRNA (SelC) was not found, nor were the genes for SelA, SelB and SelD. With the exception of Asp-$tRNA^{GTC}$ and Val-$tRNA^{CAC}$, tRNA genes are not linked in the *A. fulgidus* genome. The RNA component of the tRNA maturation enzyme RNase P is present. Both *A. fulgidus* and *M. jannaschii* appear to possess an enzyme that inserts the tRNA-modified nucleoside archaeosine, but only *A. fulgidus* has the related enzyme that inserts the modified base queuine.

Both *A. fulgidus* and *M. jannaschii* lack glutamine synthetase and asparagine synthetase; the relevant tRNAs are presumably amino-acylated with glutamic and aspartic acids, respectively. An enzymatic *in situ* transamidation then converts the amino acid to its amide form, as seen in other Archaea and in Gram-positive Eubacteria[30]. Indeed, genes for the three subunits of the Glu-tRNA amidotransferase (*gatABC*) have been identified in *A. fulgidus*. The Lys aminoacyl-tRNA synthetase in both organisms is a class I-type, not a class II-type[31]. *A. fulgidus* possesses a normal tRNA synthetase for both Cys and Ser, unlike *M. jannaschii* in which the former was not identifiable and the latter was unusual[9].

M. jannaschii has a single gene belonging to the TCP-1 chaperonin family, whereas *A. fulgidus* has two that encode subunits α and β of the thermosome. Phylogenetic analysis of the archaeal TCP-1 family indicates that these *A. fulgidus* genes arose by a recent species-specific gene duplication, as is the case for the two subunits of the *Thermoplasma acidophilum* thermosome[32] and the *Sulfolobus shibatae* rosettasome[33]. As in *M. jannaschii*, no *dnaK* gene was identified.

Biosynthesis of essential components

Like most autotrophic microorganisms, *A. fulgidus* is able to synthesize many essential compounds, including amino acids, cofactors, carriers, purines and pyrimidines. Many of these biosynthetic pathways show a high degree of conservation between *A. fulgidus* and *M. jannaschii*. These two Archaea are similar in their biosynthetic pathways for siroheme, cobalamin, molybdopterin, riboflavin, thiamin and nictotinate, the role category with greatest conservation between these two organisms being amino-acid biosynthesis. Of 78 *A. fulgidus* genes assigned to amino-acid biosynthetic pathways, at least 73 (94%) have homologues in *M. jannaschii*. For both archaeal species, amino-acid biosynthetic pathways resemble those of *Bacillus subtilis* more closely than

those of *E. coli*. For example, in *A. fulgidus* and *M. jannaschii*, tryptophan biosynthesis is accomplished by seven enzymes, TrpA, B, C, D, E, F, G as in *B. subtilis*, rather than by five enzymes, TrpA, B, C, D, E (including the bifunctional TrpC and TrpD) as found in *E. coli*.

No biotin biosynthetic genes were identified, yet biotin can be detected in *A. fulgidus* cell extracts[34], and several genes encode a biotin-binding consensus sequence. Similarly, *A. fulgidus* lacks the genes for pyridoxine biosynthesis although pyridoxine can be found in cell extracts (albeit at lower levels than seen in *E. coli* and several Archaea[34]). No gene encoding ferrochelatase, the terminal enzyme in haem biosynthesis, has been identified, although *A. fulgidus* is known to use cytochromes[34]. These cofactors may be obtained by mechanisms that we have not recognized. Although all of the enzymes required for pyrimidine biosynthesis appear to be present, three enzymes in the purine pathway (GAR transformylase, AICAR formyltransferase and the ATPase subunit of AIR carboxylase) have not been identified, presumably because they exist as new isoforms.

The Archaea share a unique cell membrane composed of ether lipids containing a glycerophosphate backbone with a 2,3-*sn* stereochemistry[35] for which there are multiple biosynthetic pathways[36]. In the case of *Halobacterium cutirubrum*, the backbone is apparently obtained by enantiomeric inversion of *sn*-glycerol-3-phosphate; in *Sulfolobus acidocaldarius* and *Methanobacterium thermoautotrophicum*, *sn*-glycerol-1-phosphate dehydrogenase builds the backbone from dihydroxyacetonephosphate. An orthologue of *sn*-glycerol-1-phosphate dehydrogenase has been identified in *A. fulgidus*, suggesting that the latter pathway is present.

Conclusions

Although *A. fulgidus* has been studied since its discovery ten years ago[1], the completed genome sequence provides a wealth of new information about how this unusual organism exploits its environment. For example, its ability to reduce sulphur oxides has been well characterized, but genome sequence data demonstrate that *A. fulgidus* has a great diversity of electron transport systems, some of unknown specificity. Similarly, *A. fulgidus* has been characterized as a scavenger with numerous potential carbon sources, and its gene complement reveals the extent of this capability. *A. fulgidus* appears to obtain carbon from fatty acids through β-oxidation, from degradation of amino acids, aldehydes and organic acids, and perhaps from CO.

A. fulgidus has extensive gene duplication in comparison with other fully sequenced prokaryotes. For example, in the fatty acid and phospholipid metabolism category, there are 10 copies of 3-hydroxyacyl-CoA dehydrogenase, 12 copies of 3-ketoacyl-CoA thiolase, and 12 of acyl-CoA dehydrogenase. The duplicated proteins are not identical, and their presence suggests considerable metabolic differentiation, particularly with respect to the pathways for decomposing and recycling carbon by scavenging fatty acids. Other categories show similar, albeit less dramatic, gene redundancy. For example, there are six copies of acetyl-CoA synthetase and four aldehyde ferredoxin oxidoreductases for fermentation, as well as four copies of aspartate aminotransferase for amino-acid biosynthesis. These observations, together with the large number of paralogous gene families, suggest that gene duplication has been an important evolutionary mechanism for increasing physiological diversity in the Archaeoglobales.

A comparison of two archaeal genomes is inadequate to assess the diversity of the entire domain. Given this caveat, it is nevertheless possible to draw some preliminary conclusions from the comparison of *M. jannaschii* and *A. fulgidus*. A comparison of the gene content of these Archaea reveals that gene conservation varies significantly between role categories, with genes involved in transcription, translation and replication highly conserved; approximately 80% of the *A. fulgidus* genes in these categories have homologues in *M. jannaschii*. Biosynthetic pathways are also highly conserved, with approximately 80% of the *A. fulgidus* biosynthetic genes having homologues in *M. jannaschii*. In contrast, only 35% of the *A. fulgidus* central intermediary metabolism genes have homologues, reflecting their minimal metabolic overlap.

Over half of the *A. fulgidus* ORFs (1,290) have no assigned biological role. Of these, 639 have no database match. The remaining 651, designated 'conserved hypothetical proteins', have sequence similarity to hypothetical proteins in other organisms, two-thirds with apparent homologues in *M. jannaschii*. These shared hypothetical proteins will probably add to our understanding of the genetic repertoire of the Archaea. Analysis of the *A. fulgidus* and other archaeal and eubacterial genomes will provide the information necessary to begin to define a core set of archaeal genes, as well as to better understand prokaryotic diversity. □

Methods

Whole-genome random sequencing procedure. The type strain, *A. fulgidus* VC-16, was grown from a culture derived from a single cell isolated by optical tweezers[37] and provided by K. O. Stetter (University of Regensburg). Cloning, sequencing and assembly were essentially as described previously for genomes sequenced by TIGR[9,38–40]. One small-insert and one medium-insert plasmid library were generated by random mechanical shearing of genomic DNA. One large-insert lambda (λ) library was generated by partial *Tsp*509I digestion and ligation to λ-DASHII/*Eco*RI vector (Stratagene). In the initial random sequencing phase, 6.7-fold sequence coverage was achieved with 27,150 sequences from plasmid clones (average read length 500 bases) and 1,850 sequences from λ-clones. Both plasmid and λ-sequences were jointly assembled using TIGR assembler[41], resulting in 152 contigs separated by sequence gaps and five groups of contigs separated by physical gaps. Sequences from both ends of 560 λ-clones served as a genome scaffold, verifying the orientation, order and integrity and the contigs. Sequence gaps were closed by editing the ends of sequence traces and/or primer walking on plasmid or λ-clones clones spanning the respective gap. Physical gaps were closed by combinatorial polymerase chain reaction (PCR) followed by sequencing of the PCR product. At the end of gap closure, 90 regions representing 0.33% of the genome had only single-sequence coverage. These regions were confirmed with terminator reactions to ensure a minimum of 2-fold sequence coverage for the whole genome. The final genome sequence is based on 29,642 sequences, with a 6.8-fold sequence coverage. The linkage between the terminal sequences of 2,101 clones from the small-insert plasmid library (average size 1,419 bp) and 8,726 clones from the medium-insert plasmid library (average size 2,954 bp) supported the genome scaffold formed by the λ-clones (average size 16,381 bp), with 96.9% of the genome covered by λ-clones. The reported sequence differs in 20 positions from the 14,389 bp of DNA in a total of 11 previously published *A. fulgidus* genes.

ORF prediction and gene family identification. Coding regions (ORFs) were identified using a combination strategy based on two programs. Initial sets of ORFs were derived with GeneSmith (H.O.S., unpublished), a program that evaluates ORF length, separation and overlap between ORFs, and with CRITICA (J.H.B. & G.J.O., unpublished), a coding region identification tool using comparative analysis. The two largely overlapping sets of ORFs were merged into one joint set containing all members of both initial sets. ORFs were searched against a non-redundant protein database using BLASTX[10] and those shorter than 30 codons 'coding' for proteins without a database match were eliminated. Frameshifts were detected and corrected where appropriate as described previously[40]. Remaining frameshifts are considered authentic and corresponding regions were annotated as 'authentic frameshift'. In total, 527 hidden Markov models, based upon conserved protein families (PFAM version 2.0), were searched with HMMER to determine ORF membership in families and superfamilies[42]. Families of paralogous genes were constructed as described previously[40]. TopPred[43] was used to identify membrane-spanning domains in proteins.

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Correspondence and requests for materials should be addressed to J.C.V. (e-mail: gaf@tigr.org). The annotated genome sequence and the gene family alignments are available on the World-Wide Web at http://www.tigr.org/tdb/mdb/afdb/afdb.html. The sequence has been deposited in GenBank with accession number AE000782.

00108946

The Ha-1a Monoclonal **Antibody For Gram- Negative Sepsis (Correspondence)**

Gazmuri, Raul J.; Mecher, Carter; Weil, Max Harry; Tanio, Craig P.; Feldman, Harold I.; Carlet, J.; Offenstadt, G.; Chastang, C.; Doyon, F.; Brun-Buisson, C.; Dhainaut, J.F.; Schlemmer, B.; Gutmann, L.; Schmidt, Gregory A.; Peled, Harry B.; Mackenzie, S.; Kinsella, J.; Young, Lowell S.; Gorelick, Kenneth J.; Baumgartner, Jean-Daniel; Heumann, Didier; Glauser, Michel-Pierre; Ziegler, Elizabeth J.; Fisher, Charles J., Jr.; Sprung, Charles L.; Smith, Craig R.; Straube, Richard C.; Sadoff, Jerald C.; Dellinger, R.-Phillip; Wolff, Sheldon M.
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TEXT

Letter 001

To the Editor: Ziegler and collaborators (Feb. 14 issue) (Ref. 1) recently reported on an impressive reduction in 28-day mortality, from 49 percent to 30 percent, in a subgroup of patients who had bacteremia due to gram-negative bacilli. The patients were treated with human anti-lipid A **monoclonal** antibody early in the course after the onset of symptoms. Patients with sepsis or bacteremia caused by microorganisms other than gram-negative bacilli received no measurable benefit. These results prompted the investigators to recommend the therapy as routine treatment for patients with clinical signs of bacteremia, provided that a gram-negative organism was suspected as the cause.

The authors deserve high praise for this important result of collaborative research. Yet we have some discomfort about recommendations for routine use of the antibody. Patients were assigned to treatment with either anti-lipid A antibody or albumin placebo, depending on the basis of a clinical diagnosis of sepsis with circulatory instability, (Ref. 2) which did not distinguish between bacteriologic causes. Accordingly, of the cohort of 543 patients, only 37 percent had both bacteremia and gram-negative organisms as the cause of bacteremia. An equal percentage had gram-negative infections without bacteremia. In 15 percent, no source of infection was identified. Accordingly, only about one third of the patients fulfilled the criterion of bacteremia due to gram-negative enteric bacilli.

The authors were forthright in presenting the finding that when all patients were taken into account, there was no reduction in mortality after treatment with anti-lipid A antibody. This exposes the reality that there was no overall benefit to patients defined by the ``sepsis syndrome.'' If patients who had both bacteremia and gram-negative bacilli as the cause of the bacteremia had been identified and received anti-lipid A antibody, mortality might well have been significantly reduced. To the contrary, the failure to show an overall benefit leaves open the possibility that the demonstrated benefit to patients with gram-negative bacteremias was counterbalanced by adverse effects in some or all of the remaining patients. We therefore would be reluctant to employ this therapy on the basis of the diagnostic criteria used by Dr. Ziegler and her collaborators.

It is apparent that successful treatment with anti-lipid A antibody is contingent on the ability to make an early diagnosis of bacteremia and to establish that the bacteremia is caused by endotoxin-producing enteric bacilli, so as to preclude risks and avoid million-dollar expenditures for a majority of patients who would be treated without evidence of benefit. The authors would have to demonstrate such methods for purposes of early life-saving treatment with lipid A antibody (Ref. 3,4). It also prompts us to rethink the diagnostic usefulness of terms such as ``sepsis syndrome'' and even ``septicemia,'' in favor of bedside diagnoses with more clinical and microbiologic precision as previously suggested by our group (Ref. 5).

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Letter 002

To the Editor: The discrepancy between the patient subgroups in the

study by Ziegler et al may be explained by the possibility that HA-1A is toxic to some patients. Of the 331 patients without gram-negative bacteremia (201 of them with gram-negative infection), 141 died, for an overall mortality of 43 percent. Seventy-three of the deaths occurred among the 181 patients who received placebo (40 percent mortality), and 68 deaths occurred among the 150 who received HA-1A (45 percent mortality). This trend toward increased mortality among patients without gram-negative bacteremia in the treatment group raises the question of whether HA-1A may be seriously toxic in a large proportion of patients presenting with sepsis.

At present, there is no method of identifying a priori the patients presenting with sepsis in whom gram-negative bacteremia will develop. Therefore, the early clinical use of HA-1A will necessitate treating many patients without gram-negative bacteremia. This would result in the treatment of many patients in whom it has no proved benefit and, perhaps, in whom it would be toxic. Before HA-1A gains widespread acceptance for the treatment of sepsis, additional effort should be made to identify predictors of subgroups of patients with sepsis who would be most likely to benefit from this agent. Such predictors could be based on the clinical characteristics of patients at presentation; their use would reduce the number of patients unnecessarily exposed to HA-1A, thereby reducing potential adverse consequences of drug administration and increasing its cost effectiveness. Craig P. Tanio, M.D., Harold I. Feldman, M.D. Hospital of the University of Pennsylvania Philadelphia, PA 19104

Letter 003

To the Editor: In the study by Ziegler et al., it is extremely important that the placebo-treated patients and the HA-1A-treated patients in the subgroup with gram-negative bacteremia should be strictly comparable. Unfortunately, there is obviously an imbalance between the two treatment groups. The placebo-treated patients were older (62.3 vs. 58 years) and had higher rates of organ-system failure, with a difference of 3 percent for disseminated intravascular coagulation, 4 percent for adult respiratory distress syndrome, 7 percent for acute hepatic failure, and 11 percent for acute renal failure. Only 87 percent of the placebo recipients were given adequate antibiotic therapy, as opposed to 93 percent of the HA-1A recipients. All these ``differences,'' even if not statistically significant according to univariate analysis, go in the same direction, favoring the HA-1A recipients. Accordingly, the score for the Acute Physiology and Chronic Evaluation System (APACHE II score), which correlates with mortality, was higher in the placebo group than in the HA-1A group (25.7 vs. 23.6).

A multivariate approach is mandatory here, and the results of the Cochran-Mantel-Haenszel test are of considerable importance. The authors argued that the difference in mortality remains ``significant,'' but it is necessary to know whether this difference remained significant or became markedly reduced after adjustment. Besides, it is unclear whether all the possible confounding factors were taken into account in this analysis.

It is also unclear why HA-1A should be effective in patients with the sepsis syndrome who have bacteremia but not in those with the syndrome who do not have bacteremia, since endotoxin, even in the latter group, is likely to be responsible for multiple organ failure and septic shock. Moreover, the study did not demonstrate any correlation between bacteremia and mortality. On the contrary, several studies have shown an inverse correlation.* ----------

*: Calandra T, Baumgartner J-D, Grau GE, et al Prognostic values of tumor necrosis factor/cachectin, interleukin-1, interferon-alpha, and interferon-gamma in the serum of patients with septic shock. J Infect Dis 1990; 161:982-7.

In conclusion, even if the study by Ziegler et al supports a reasonable presumption of the efficacy of HA-1A, for evident ethical, scientific, and economic reasons we need other studies to confirm the efficacy of treatment with this antibody before it comes into routine use for patients in whom severe gram-negative sepsis is suspected. J. Carlet, M.D. Hopital Saint-Joseph 75674 Paris, France G. Offenstadt, M.D. Hopital Saint-Antoine 75012 Paris, France C. Chastang, M.D. Hopital Saint-Louis 75010 Paris, France F. Doyon, M.D. Institut Gustave Roussy 94800 Villejuif, France C. Brun-Buisson, M.D. Hopital Henri Mondor 94000 Creteil, France J.F. Dhainaut, M.D. Hopital Cochin 75014 Paris, France B. Schlemmer, M.D. Hopital Saint-Louis 75010 Paris, France L. Gutmann, M.D. Hopital Broussais

75015 Paris, France

Letter 004

' To the Editor: A crucial point about the study of HA-1A reported by · Dr. Ziegler and colleagues is that when the results for all patients meeting the entry criteria were analyzed, there was no difference in outcome between those given HA-1A and those given placebo (P = 0.24). Although there was clear benefit to certain subgroups (patients with documented gram-negative bacteremia, with or without shock), a treating physician does not know what the culture results for a given patient will be until 48 hours or more after the patient's blood has been drawn. The dilemma, then, is that clinicians can choose to give this new therapy to all patients whose condition meets the definition of ``sepsis'' (knowing that their outcomes are not significantly different whether they receive the antibody or placebo), wait to treat only the patients whose blood cultures become positive (a potentially lethal delay), or attempt to devise better criteria to identify patients who will have gram-negative bacteremia (an unlikely feat). Since the new **monoclonal** - antibody therapy is likely to cost more than $2,000 per patient treated, this question is not academic.

In his editorial accompanying the article by Ziegler et al., Dr. Wolff reminds us that gram-negative bacteremia develops in 100,000 to 300,000 patients in the United States each year.* Since only 200 patients in the HA-1A study had gram-negative bacteremia and 543 patients met the entry criteria, up to 800,000 patients could be eligible for treatment with HA-1A at an annual cost of up to $1.6 billion. Individual physicians will certainly prescribe this apparently nontoxic magic bullet for their patients unless constrained by local pharmacy and therapeutics committees, private insurers, government, or advice from expert physicians. I for one would have valued Wolff's opinion regarding the applicability of the HA-1A study to clinical practice. ----------

*: Wolff Sm. **Monoclonal** antibodies and the treatment of gram-negative bacteremia and shock. N Engl J Med 1991; 324:486-8. Gregory A. Schmidt, M.D. University of Chicago Chicago, IL 60637

To the Editor: The conclusions of Ziegler et al are not in concordance with their data. Although the HA-1A **monoclonal** antibody showed rather impressive effects in reducing the mortality in patients who turned out to have gram-negative bacteremia, there was no difference in survival overall in the entire group that was treated. Nowhere in the article do the authors offer any information about how one may determine which patients initially admitted with suspected gram-negative bacteremia will turn out to have positive blood cultures. This information is not known when one decides to treat a patient. The authors concluded that ``empirical immunotherapy with HA-1A should be considered in] patients with suspected gram-negative infection presenting] with sepsis.'' Their data, however, clearly showed that when patients were treated with this therapy, there was absolutely no statistically significant difference in mortality (P = 0.24).

Until a better marker for determining the early presence of gram-negative bacteremia is found, the data indicate absolutely no role for this antibody at present in the treatment of patients with suspected gram-negative sepsis. Harry B. Peled, M.D., F.A.C.C. Fhp Hospital Fountain Valley, CA 92708

Letter 005

To the Editor: . . . We are concerned that in their analysis of treatment safety Ziegler et al reported that 291 patients received HA-1A and in their analysis of mortality they reported that 262 received it. No explanation is given for this discrepancy. It would clearly be of importance in interpreting the results of the trial if a number of patients were not included in the statistical analysis. S. Mackenzie, M.B., F.C.Anaes., J. Kinsella, M.B., F.C.Anaes. Royal Infirmary Glasgow G4 0sf, Scotland

Letter 006

To the Editor: In his thoughtful editorial on the treatment of gram-negative sepsis with **monoclonal** antibodies, Dr. Wolff referred to data from clinical trials of E5, an anti-lipid A **monoclonal** antibody (Ref. 1). Although in general we agree with his discussion, we would like to correct two statements made about the E5 antibody.

First, the antibody was referred to as `` **humanized** .'' In fact, E5 is not **humanized** , but is a purely murine product. It was developed by fusing splenocytes from mice immunized against the J5 mutant of Escherichia coli

with murine myeloma cells (Ref. 2). The initial report by Teng et al (Ref. 3). clearly states that HA-1A originated as the product of fusion between human spleen cells and a mouse-human heteromyeloma. In addition, for the two antibodies under discussion, the distinction between human and murine origins may be more theoretical than real. The half-life of E5 (18 hours) (Ref. 4) and that of HA-1A (16 hours) (Ref. 5) are similar in humans, but both differ substantially from the 5-day half-life of native human IgM (Ref. 6). This is understandable in the case of E5, which is murine. In the case of HA-1A, this difference may be explained by its synthesis and glycosylation in a mouse-human heteromyeloma, (Ref. 3) which may result in its more closely resembling a murine antibodySecond, the survival benefit associated with E5 treatment of patients with gram-negative sepsis cited in the preliminary report (Ref. 1) was not limited to patients with bacteremia, as stated by Wolff, but also included patients with gram-negative sepsis documented by culture of bacteria from an infected body site in the absence of a positive blood culture. Since blood cultures are positive in only 50 percent of patients with gram-negative sepsis, (Ref. 7) this is an important distinction. Furthermore, a recent study showed that endotoxin, the target of anti-endotoxin antibodies, was recovered more frequently from the blood of patients with sepsis who did not have bacteremia than from those who did (Ref. 8). Thus, conclusions about treatment of gram-negative sepsis with an anti-endotoxin antibody whose beneficial effects are limited to patients with positive blood cultures may not be generally applicable to therapy with anti-endotoxin antibodies that benefit a broader range of patients.

Adjunctive immunotherapy of gram-negative sepsis may be an important advance in the care of critically ill patients. We agree with Wolff that additional investigation is required before physicians can determine which patients may benefit from its application. Lowell S. Young, M.D. Kuzell Institute San Francisco, CA 94115 Kenneth J. Gorelick, M.D. XOMA Corporation Berkeley, Ca 94710

(Dr. Young is a consultant to XOMA Corporation, the manufacturer of the E5 antibody, and Dr. Gorelick is a shareholder and an employee).

Letter 007

To the Editor: . . . After Teng et al (Ref. 1). reported that hybridoma fluid containing HA-1A was protective in mice and rabbits, cells isolated from the original clone were licensed to two companies: Centocor (Malvern, Pa.), the organizer of the clinical study by Ziegler et al., (Ref. 2) and Merieux (Lyon, France). Using purified **monoclonal** antibody instead of hybridoma fluid, neither Merieux Laboratories nor we could reproduce protection against gram-negative bacteria or endotoxin (Ref. 3) in models similar to those of Teng et al (Ref. 1). Lipopolysaccharide-induced tumor necrosis factor was not suppressed in vitro or in vivo by this **monoclonal** antibody (Ref. 3). The antibody bound moderately to lipid A and Re lipopolysaccharide, but poorly to lipopolysaccharide from pathogenic smooth gram-negative bacteria. The apparent affinity constants (Ref. 4) for two types of lipid A (isolated from Salmonella minnesota R595 and from Pseudomonas aeruginosa 220) were lower than 10(sup 4) M(sup 1). The **monoclonal** antibody bound to a large range of gram-negative bacteria and also to **gram - positive** bacteria, to fungi, and to lipids unrelated

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L12: Entry 13 of 18 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962291 A
TITLE: Metal dependent catalytic antibodies and method for producing the same

Brief Summary Text (18):
To date, research in the field of metal dependent catalytic antibody induction is based entirely on using transition state analogues as haptens. This approach to generating catalytic antibodies however is problematic for the hydrolysis of phosphodiesters. The transition state for phosphodiester bond hydrolysis is trigonal trigonal pyramidal; that is, 5-coordinate. The classical approach to generating catalytic antibodies for phosphodiester bond hydrolysis would be to synthesize a suitably stable 5-coordinate compound for use as a hapten and screen the resulting antibodies for catalytic activity. Unfortunately, phosphorus does not form stable 5-coordinate complexes that resemble this transition state. Other elements, such as vanadium (V), with this geometry are too unstable in aqueous solutions and would be hydrolyzed before an immune response could be mounted. Currently there is no known catalytic antibody that can hydrolyze phosphodiester bonds, nor are there any known catalytic antibodies that can independently bind a metal ion that acts as a cofactor in a chemical reaction.

Brief Summary Text (19):
There is still a need, therefore, for catalytic antibodies and a method for producing catalytic antibodies that are capable of hydrolyzing phosphodiester bonds in a metal dependent manner.

Brief Summary Text (23):
It is still a further object of this invention to generate catalytic antibodies capable of hydrolyzing phosphodiester bonds in a metal dependent manner.

Detailed Description Text (2):
In general, the catalytic antibodies and method for inducing catalytic antibodies according to this invention do not rely on the classical transition state analogue approach, but rather depend directly on eliciting antibodies to a hapten in the form of a stable derivative of a phosphodiester substrate capable of chelating metal ions. Such a hapten is not possible with normal phosphodiester bonds since their affinity for free metal ions is either low or the resulting complexes are hydrolytically unstable. Hence, the preferred embodiment of the present invention comprises a hapten having the two non-bridging oxygens of the phosphodiester bond replaced by sulfur thereby producing a phosphorodithioate analogue hapten. This phosphorodithioate hapten of the present invention is then attached to a carrier protein to produce an antigen prior to immunization.

Detailed Description Text (84):
Phosphodiester Substrate. Antibody 6A1A6 of the present invention was found to catalyze the hydrolysis of thymidine-5'-monophosphate-p-nitrophenyl ester (pNPPT) in a metal dependent fashion. This represents the first report of a catalytic antibody capable of hydrolyzing a phosphodiester bond. pNPPT is normally used as a substrate for snake venom phosphodiesterase. The apparent values of k.sub.cat and K.sub.m with 10 mM MgCl.sub.2 were 0.031.+-.0.05 min.sup.-1, and 0.29.+-.0.08 mM, respectively. See FIG. 8a. The uncatalyzed rate under these conditions was

1.35.times.10.sup.-6 min.sup.-1. The antibody was found to undergo at least 16 turnovers before a reduction in velocity was seen, due to inhibition of the reaction reaction by the product p-nitrophenol (pnp). The K.sub.i for p-nitrophenol determined from a Dixon plot was 10.1.+-.2.1 .mu.M shown in FIG. 8b. The K.sub.i is defined as the negative x-coordinate of the intersection point of the lines in a Dixon plot.

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☐ 6. 20020119459. 29 Jun 01. 29 Aug 02. Optical sorting method. Griffiths, Andrew. 435/6; 264/4.1 435/7.1 C12Q001/68 G01N033/53 B01J013/02 B01J013/04.

☐ 7. 20020025550. 02 Jul 01. 28 Feb 02. Methods for producing highly phosphorylated lysosomal hydrolases. Canfield, William M.. 435/68.1; 424/94.61 435/201 C12P021/06 A61K038/47 C12N009/26.

☐ 8. 6670165. 09 Nov 01; 30 Dec 03. Methods for producing highly phosphorylated lysosomal hydrolases. Canfield; William M.. 435/195;. C12N009/14.

☐ 9. 6642038. 10 Aug 00; 04 Nov 03. GlcNAc phosphotransferase of the lysosomal targeting pathway. Canfield; William M.. 435/195; 435/194 435/252.3 435/320.1 536/23.2. C12N009/14 C12N009/12 C12N001/20 C12N015/00 C07H021/04.

☐ 10. 6537785. 10 Aug 00; 25 Mar 03. Methods of treating lysosomal storage diseases. Canfield; William M.. 424/94.61; 424/94.1 435/195 435/200 435/41 435/74. A61K038/47.

☐ 11. 6534300. 10 Aug 00; 18 Mar 03. Methods for producing highly phosphorylated lysosomal hydrolases. Canfield; William M.. 435/195; 435/194. C12N009/14 C12N009/12.

☐ 12. 6300308. 30 Dec 98; 09 Oct 01. Methods and compositions for inducing autoimmunity in the treatment of cancers. Schroit; Alan J.. 514/8; 424/193.1 424/278.1. A61K038/16 A61K039/385 A61K045/00.

☐ 13. 5962291. 10 Oct 97; 05 Oct 99. Metal dependent catalytic antibodies and method for

producing the same. Graff; Darla A., et al. 435/188.5; 435/346 530/388.9. C12N009/00 C12N005/12.

☐ 14. 5391723. 16 Feb 93; 21 Feb 95. Oligonucleotide conjugates. Priest; John H.. 536/23.1; 530/402. C07H015/12.

☐ 15. 5314817. 10 Dec 92; 24 May 94. Catalytic and reactive polypeptides and methods for their preparation and use. Schultz; Peter. 435/188.5; 530/388.9 530/389.8. C12N009/00.

☐ 16. 5302516. 10 Dec 92; 12 Apr 94. Catalytic and reactive polypeptides and methods for their preparation and use. Schultz; Peter. 435/41; 435/188.5. C12N009/00 C12P001/00.

☐ 17. 5215889. 08 Sep 89; 01 Jun 93. Catalytic and reactive polypeptides and methods for their preparation and use. Schultz; Peter. 435/41; 435/183 435/188.5 435/195 435/196 530/387.1. C12N009/00 C12P001/00.

☐ 18. 4963355. 19 Jun 87; 16 Oct 90. Production of antibody catalysts. Kim; Peter S., et al. 435/188.5; 424/141.1 424/175.1 424/94.1 435/183 435/68.1 436/518 436/537 436/547 436/548 436/821 530/388.9 530/389.8 530/808. C12Q001/44 A61K039/00 C07F009/40 C07F009/65.

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Terms	Documents
antibod$ near5 phosphodiester	18

Prev Page Next Page Go to Doc#

First Hit

L12: Entry 1 of 18 File: PGPB Oct 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030185820
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030185820 A1

TITLE: Protein belonging to the TNF superfamily involved in signal transduction, nucleic acids encoding same, and methods of use thereof

PUBLICATION-DATE: October 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Choi, Yongwon	New York	NY	US	
Wong, Brian	New York	NY	US	
Josien, Regis	New York	NY	US	
Steinman, Ralph	Westport	CT	US	

APPL-NO: 09/ 873829 [PALM]
DATE FILED: May 9, 2002

RELATED-US-APPL-DATA:
Application 09/873829 is a continuation-in-part-of US application 09/210115, filed December 11, 1998, ABANDONED
Application 09/210115 is a continuation-in-part-of US application 09/034099, filed March 3, 1998, ABANDONED
Application 09/034099 is a continuation-in-part-of US application 08/989479, filed December 12, 1997, ABANDONED
Application is a non-provisional-of-provisional application 60/069589, filed December 12, 1997,

INT-CL: [07] A61 K 48/00, A61 K 39/395, C12 Q 1/68, C07 H 21/04, C12 P 21/02, C12 N 5/06, C07 K 14/705, C07 K 16/28

US-CL-PUBLISHED: 424/143.1; 514/44, 424/93.21, 530/388.22, 536/23.5, 435/6, 435/69.1, 435/320.1, 530/350
US-CL-CURRENT: 424/143.1; 424/93.21, 435/320.1, 435/6, 435/69.1, 514/44, 530/350, 530/388.22, 536/23.5

REPRESENTATIVE-FIGURES: 1

ABSTRACT:

A method of modulating immune response in an animal is disclosed. Such a method interacting the immature dendritic cels from the animal with an antigen ex vivo so that the immature dendritic cells present the antigen on their surfaces, inducing maturation of the immature dendritic cells ex vivo, and contacting the mature dendritic cells ex vivo with a modulator comprising TRANCE, conservative variants thereof, fragments thereof, analogs or derivatives thereof, or a fusion protein comprising the amino acid sequence of TRANCE, conservative variants thereof, or

fragments thereof. After contacting the modulator ex vivo, the mature dendritic cells are introduced into the animal. As a result, immune response in the animal towards the antigen is modulated relative to the immune response against the antigen antigen in an animal in which dendritic cells did not interact with the antigen ex vivo, and did not contact a modulator ex vivo. Preferably, the method of the present present invention results in increasing immune response towards the antigen in the animal.

DOMESTIC PRIORITY CLAIM

[0001] The priority is claimed of U.S. Provisional Application No. 60069,589 filed on Dec. 12, 1997, which is hereby incorporated by reference herein in its entirety.

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YSTEM:OS  - DIALOG OneSearch
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E4      597  LIPOTEICHOIC ACID
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E6        3  LIPOTEICHOIC ACID RECEPTOR
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              3  S3
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           2252  HUMANIZ?
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?t s6/9/all

 6/9/1
DIALOG(R)File 155:MEDLINE(R)
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12437678   PMID: 12847223
  Pattern recognition by TREM-2: binding of anionic ligands.
  Daws Michael R; Sullam Paul M; Niemi Erene C; Chen Thomas T; Tchao Nadia
K; Seaman William E
  Department of Immunology and Division of Infectious Diseases, Veterans
Affairs Medical Center and University of California, San Francisco, CA
94121, USA. mdaws@itsa.ucsf.edu
  Journal of immunology (Baltimore, Md. - 1950) (United States) Jul 15
2003, 171 (2) p594-9, ISSN 0022-1767 Journal Code: 2985117R
  Contract/Grant No.: AI41513; AI; NIAID; R01 CA87922-01A1; CA; NCI
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Subfile:  AIM; INDEX MEDICUS
  We recently described the cloning of murine triggering receptor expressed
by myeloid cells (TREM) 2, a single Ig domain DNAX adaptor protein
12-associated receptor expressed by cells of the myeloid lineage. In this
study, we describe the identification of ligands for TREM-2 on both
bacteria and mammalian cells. First, by using a TREM-2A/IgG1-Fc fusion
protein, we demonstrate specific binding to a number of Gram-negative and
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Gram-positive bacteria and to yeast. Furthermore, we show that fluorescently labeled Escherichia coli and Staphylococcus aureus bind specifically to TREM-2-transfected cells. The binding of TREM-2A/Ig fusion protein to E. coli can be inhibited by the bacterial products LPS, **lipoteichoic** acid, and peptidoglycan. Additionally, binding can be inhibited by a number of other anionic carbohydrate molecules, including dextran sulfate, suggesting that ligand recognition is based partly on charge. Using a sensitive reporter assay, we demonstrate activation of a TREM-2A/CD3zeta **chimeric** receptor by both bacteria and dextran sulfate. Finally, we demonstrate binding of TREM-2A/Ig fusion to a series of human astrocytoma lines but not to a variety of other cell lines. The binding to astrocytomas, like binding to bacteria, is inhibited by anionic bacterial products, suggesting either a similar charge-based ligand recognition method or overlapping binding sites for recognition of self- and pathogen-expressed ligands.

Tags: Comparative Study; Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Descriptors: *Receptors, Immunologic--metabolism--ME; Animals; Anions; Astrocytoma--metabolism--ME; Astrocytoma--microbiology--MI; Bacterial Adhesion--drug effects--DE; Bacterial Adhesion--genetics--GE; Bacterial Adhesion--immunology--IM; Binding, Competitive--genetics--GE; Binding, Competitive--immunology--IM; **Chimeric** Proteins --antagonists and inhibitors--AI; **Chimeric** Proteins--metabolism--ME; Dextran Sulfate --pharmacology--PD; Gram-Negative Bacteria--physiology--PH; Gram-Positive Bacteria--physiology--PH; Immunoglobulins, Fc--genetics--GE; Immunoglobuli ns, Fc--metabolism--ME; Jurkat Cells; Leukemia P388; Ligands; Lipopolysaccharides--pharmacology--PD; Mice; Peptidoglycan--pharmacology --PD; Protein Binding--drug effects--DE; Protein Binding--genetics--GE; Protein Binding--immunology--IM; Receptors, Immunologic--biosynthesis--BI; Receptors, Immunologic--genetics--GE; Receptors, Immunologic--physiology --PH; Solubility; Teichoic Acids--pharmacology--PD; Transfection; Tumor Cells, Cultured

CAS Registry No.: 0 (Anions); 0 (Chimeric Proteins); 0 (Immunoglobulins, Fc); 0 (Ligands); 0 (Lipopolysaccharides); 0 (Peptidoglycan); 0 (Receptors, Immunologic); 0 (TREM-2a receptor); 0 (TREM-2b receptor); 0 (Teichoic Acids); 0 (Trem3 protein, mouse); 56411-57-5 (lipoteichoic acid); 9042-14-2 (Dextran Sulfate)

Record Date Created: 20030708

Record Date Completed: 20031023

6/9/2

DIALOG(R)File 155:MEDLINE(R)

12418828 PMID: 12684515

Cell wall attachment of a widely distributed peptidoglycan binding domain is hindered by cell wall constituents.

Steen Anton; Buist Girbe; Leenhouts Kees J; El Khattabi Mohamed; Grijpstra Froukje; Zomer Aldert L; Venema Gerard; Kuipers Oscar P; Kok Jan

Department of Genetics, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Kerklaan 30, 9751 NN Haren, The Netherlands.

Journal of biological chemistry (United States) Jun 27 2003, 278 (26) p23874-81, ISSN 0021-9258 Journal Code: 2985121R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

The C-terminal region (cA) of the major autolysin AcmA of Lactococcus lactis contains three highly similar repeated regions of 45 amino acid residues (LysM domains), which are separated by nonhomologous sequences. The cA domain could be deleted without destroying the cell wall-hydrolyzing activity of the enzyme in vitro. This AcmA derivative was capable neither of binding to lactococcal cells nor of lysing these cells while separation of the producer cells was incomplete. The cA domain and a **chimeric** protein consisting of cA fused to the C terminus of MSA2, a malaria parasite surface antigen, bound to lactococcal cells specifically via cA.

The fusion protein also bound to many other Gram-positive bacteria. By chemical treatment of purified cell walls of L. lactis and Bacillus subtilis, peptidoglycan was identified as the cell wall component interacting with cA. Immunofluorescence studies showed that binding is on specific locations on the surface of L. lactis, Enterococcus faecalis, Streptococcus thermophilus, B. subtilis, Lactobacillus sake, and Lactobacillus casei cells. Based on these studies, we propose that LysM-type repeats bind to peptidoglycan and that binding is hindered by other cell wall constituents, resulting in localized binding of AcmA. **Lipoteichoic** acid is a candidate hindering component. For L. lactis SK110, it is shown that **lipoteichoic** acids are not uniformly distributed over the cell surface and are mainly present at sites where no MSA2cA binding is observed.

Tags: Support, Non-U.S. Gov't

Descriptors: *Cell Wall--chemistry--CH; *Gram-Positive Bacteria --chemistry--CH; *Peptidoglycan--chemistry--CH; Bacillus subtilis --chemistry--CH; Bacillus subtilis--ultrastructure--UL; Binding Sites; Cell Wall--metabolism--ME; Enterococcus faecalis--chemistry--CH; Enterococcus faecalis--ultrastructure--UL; Gram-Positive Bacteria --ultrastructure--UL; Lactobacillus--chemistry--CH; Lactobacillus --ultrastructure--UL; Lactococcus lactis--chemistry--CH; Lactococcus lactis--ultrastructure--UL; Muramidase--metabolism--ME; Peptidoglycan --metabolism--ME; Protein Binding; Protein Structure, Tertiary; Repetitive Sequences, Nucleic Acid; Streptococcus--chemistry--CH; Streptococcus --ultrastructure--UL

CAS Registry No.: 0 (Peptidoglycan)

Enzyme No.: EC 3.2.1.- (AcmA protein, Lactococcus lactis); EC 3.2.1.17 (Muramidase)

Record Date Created: 20030623

Record Date Completed: 20030820

Date of Electronic Publication: 20030408

6/9/3

DIALOG(R)File 155:MEDLINE(R)

11423953 PMID: 11521061

Co-operative induction of pro-inflammatory signaling by Toll-like receptors.

Ozinsky A; Smith K D; Hume D; Underhill D M

Department of Immunology, University of Washington, Seattle, Washington, USA.

Journal of endotoxin research (England) 2000, 6 (5) p393-6, ISSN 0968-0519 Journal Code: 9433350

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

Toll-like receptors (TLRs) mediate detection of a broad range of pathogens and pathogen-derived products including LPS, peptidoglycan, bacterial lipopeptides, and **lipoteichoic** acid. Recent evidence indicates that the broad specificity of TLRs may be a consequence of the interactions between different TLRs. In this report, we demonstrate that while a constitutively active TLR4 homodimer can induce the production of pro-inflammatory cytokines, homodimers of TLR2 and TLR6 cannot. However, when co-expressed in the same cell, constitutively active TLR2 and TLR6 strongly induce cytokine production, indicating that these TLRs require partners to productively signal. Since TLR4 signals as a homodimer, while TLR2 and TLR6 do not, it is clear that, despite the conservation of their cytoplasmic signaling domains, the mechanisms by which they initiate signaling are different. We have localized the region of TLR4 that mediates its ability to signal as a homodimer to the membrane-proximal half of the cytoplasmic tail of the receptor.

Descriptors: *Drosophila Proteins; *Inflammation Mediators--immunology --IM; *Membrane Glycoproteins--immunology--IM; *Receptors, Cell Surface --immunology--IM; Animals; CHO Cells; Cell Line; **Chimeric** Proteins --chemistry--CH; **Chimeric** Proteins--genetics--GE; **Chimeric** Proteins

--immunology--IM; Dimerization; Hamsters; Inflammation Mediators--chemistry --CH; Luciferase--genetics--GE; Membrane Glycoproteins--chemistry--CH; Membrane Glycoproteins--genetics--GE; Mice; Receptors, Cell Surface --chemistry--CH; Receptors, Cell Surface--genetics--GE; Signal Transduction; Transfection

CAS Registry No.: 0 (Chimeric Proteins); 0 (Drosophila Proteins); 0 (Inflammation Mediators); 0 (Membrane Glycoproteins); 0 (Receptors, Cell Surface); 0 (Tehao protein, Drosophila); 0 (Toll-like receptors)

Enzyme No.: EC 1.13.12.- (Luciferase)

Record Date Created: 20010824

Record Date Completed: 20011011

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S6	1053852	MONOCLON?
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8/9/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10002130 PMID: 8122730
Monoclonal **antibodies--immunotherapy for the critically ill.**
Peake S
Renal Department, Queen Elizabeth Hospital, Woodville, South Australia.
Anaesthesia and intensive care (AUSTRALIA) Dec 1993, 21 (6) p739-51, ISSN 0310-057X Journal Code: 0342017
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS; NURSING
Monoclonal antibodies (mAb) have revolutionised many areas of medicine, particularly research and diagnostics. Murine, human and **humanized** mAb have all been developed. The most important clinical applications to date have been in the fields of transplantation and oncology. Experimental and limited clinical trials suggest mAb are emerging as a new therapeutic strategy in the critically ill. Antibodies against a variety of bacteria or their products are potentially useful in **gram** - **positive** and **gram** -negative shock. Anti-cytokine and anti-neutrophil adhesion molecule mAb may be effective not only in septic shock but also in other conditions associated with acute inflammation and cytokine release, e.g., acid aspiration, ischaemia/reperfusion injury (myocardial infarction, haemorrhagic shock, aortic aneurysm repair). Antibodies inhibiting neutrophil adhesion may also be efficacious in asthma, pulmonary fibrosis, meningitis and cerebral malaria. The use of these and other mAb in intensive care is an exciting prospect and future clinical studies will determine the extent of their role in the management of the critically ill. (175 Refs.)
Tags: Human; Support, Non-U.S. Gov't
Descriptors: Antibodies, **Monoclonal** --therapeutic use--TU; *Critical Illness; *Immunotherapy; Animals; Antibodies, Bacterial--therapeutic use --TU; Cell Adhesion Molecules--immunology--IM; Cytokines--immunology--IM; Mice
CAS Registry No.: 0 (Antibodies, Bacterial); 0 (Antibodies, Monoclonal); 0 (Cell Adhesion Molecules); 0 (Cytokines)
Record Date Created: 19940404
Record Date Completed: 19940404

8/9/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014467175 BIOSIS NO.: 200300435894
Opsonic and protective monoclonal **and chimeric antibodies specific for lipoteichoic acid of** gram positive **bacteria**
AUTHOR: Fischer Gerald W (Reprint); Schuman Richard F; Wong Hing; Stinson Jeffrey R
AUTHOR ADDRESS: Bethesda, MD, USA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1273 (4): Aug. 26, 2003 2003

MEDIUM: e-file
PATENT NUMBER: US 6610293 PATENT DATE GRANTED: August 26, 2003 20030826
PATENT CLASSIFICATION: 424-1331 PATENT ASSIGNEE: The Henry M. Jackson Foundation for the Advancement of Military Medicine; Sunol Molecular Corporation PATENT COUNTRY: USA
ISSN: 0098-1133 _(ISSN print)
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention encompasses **monoclonal** and chimeric antibodies that bind to lipoteichoic acid of **Gram positive** bacteria. The antibodies also bind to whole bacteria and enhance phagocytosis and killing of the bacteria in vitro and enhance protection from lethal infection in vivo. The mouse **monoclonal** antibody has been **humanized** and the resulting chimeric antibody provides a previously unknown means to diagnose, prevent and/or treat infections caused by **gram positive** bacteria bearing lipoteichoic acid. This invention also encompasses a peptide mimic of the lipoteichoic acid epitope binding site defined by the **monoclonal** antibody. This epitope or epitope peptide mimic identifies other antibodies that may bind to the lipoteichoic acid epitope. Moreover, the epitope or epitope peptide mimic provides a valuable substrate for the generation of vaccines or other therapeutics.

REGISTRY NUMBERS: 9041-38-7: lipoteichoic acid
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology
BIOSYSTEMATIC NAMES: Bacteria--Microorganisms
ORGANISMS: **gram positive** bacteria (Bacteria)--pathogen
COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms
DISEASES: bacterial infection--bacterial disease
MESH TERMS: Bacterial Infections (MeSH)
CHEMICALS & BIOCHEMICALS: chimeric antibodies--antibacterial-drug, antiinfective-drug; lipoteichoic acid; opsonic **monoclonal** antibodies --antibacterial-drug, antiinfective-drug
CONCEPT CODES:
12512 Pathology - Therapy
22002 Pharmacology - General
31000 Physiology and biochemistry of bacteria
38502 Chemotherapy - General, methods and metabolism
38504 Chemotherapy - Antibacterial agents
BIOSYSTEMATIC CODES:
05000 Bacteria

8/9/14 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008947781 BIOSIS NO.: 199396112197
A modified enzyme-linked immunosorbent assay for measuring type-specific anti-pneumococcal capsular polysaccharide antibodies
AUTHOR: Konradsen Helle Bossen (Reprint); Sorensen Uffe B Skov; Henrichsen Jorgen
AUTHOR ADDRESS: Dep. Bacteriol., Div. Diagnostic Microbiol., Statens Seruminstitut, Artillerivej 5, 2300 Copenhagen S, Denmark**Denmark
JOURNAL: Journal of Immunological Methods 164 (1): p13-20 1993
ISSN: 0022-1759
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have developed an ELISA for antibody determination, superior to others hitherto described, in which optimal coating is achieved using phenylated pneumococcal capsular polysaccharides as coating antigen. The specificity of the assay is ensured by complete inhibition by antibodies against the species-specific pneumococcal antigen, C-polysaccharide (C-Ps). The method is sensitive, specific, reproducible, fast and easy to work with and can be used for both immunoglobulin class and subclass

antibody determinations.

DESCRIPTORS:
MAJOR CONCEPTS: Clinical Endocrinology--Human Medicine, Medical Sciences; Hematology--Human Medicine, Medical Sciences; Immune System--Chemical Coordination and Homeostasis; Infection; Metabolism; Pathology; Pharmacology
BIOSYSTEMATIC NAMES: **Gram** - **Positive** Cocci--Eubacteria, Bacteria, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: **gram** - **positive** cocci (**Gram** - **Positive** Cocci); Peptostreptococcus magnus (**Gram** - **Positive** Cocci); human (Hominidae); mouse (Muridae
COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
MISCELLANEOUS TERMS: AFFINITY CHROMATOGRAPHY; CHIMERIC RECOMBINANT ANTIBODY; FAB FRAGMENT; FV FRAGMENT; GENETIC ENGINEERING; **HUMANIZED** ANTIBODY; IMMUNOGLOBULIN A; IMMUNOGLOBULIN G; IMMUNOGLOBULIN M; IMMUNOLOGIC METHOD; **MONOCLONAL** ANTIBODY; PURIFICATION METHOD
CONCEPT CODES:
10054 Biochemistry methods - Proteins, peptides and amino acids
10064 Biochemistry studies - Proteins, peptides and amino acids
10068 Biochemistry studies - Carbohydrates
10804 Enzymes - Methods
12504 Pathology - Diagnostic
13012 Metabolism - Proteins, peptides and amino acids
13020 Metabolism - Metabolic disorders
15006 Blood - Blood, lymphatic and reticuloendothelial pathologies
22005 Pharmacology - Clinical pharmacology
22018 Pharmacology - Immunological processes and allergy
34502 Immunology - General and methods
34504 Immunology - Bacterial, viral and fungal
34508 Immunology - Immunopathology, tissue immunology
36002 Medical and clinical microbiology - Bacteriology
BIOSYSTEMATIC CODES:
07700 **Gram** - **Positive** Cocci
86215 Hominidae
86375 Muridae

8/9/15 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008947780 BIOSIS NO.: 199396112196
Purification of antibodies using protein L-binding framework structures in the light chain variable domain
AUTHOR: Nilson Bo H K (Reprint); Logdberg Lennart; Kastern William; Bjorck Lars; Akerstrom Bo
AUTHOR ADDRESS: Dep. Med. Physiol. Chem., Univ. Lund, P.O. Box 94, S-221 00 Lund, Sweden**Sweden
JOURNAL: Journal of Immunological Methods 164 (1): p33-40 1993
ISSN: 0022-1759
DOCUMENT TYPE: Meeting
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein L from the bacterial species Peptostreptococcus magnus binds specifically to the variable domain of Ig light chains, without interfering with the antigen-binding site. In this work a genetically engineered fragment of protein L, including four of the repeated Ig-binding repeat units, was employed for the purification of Ig from various sources. Thus, IgG, IgM, and IgA were purified from human and mouse serum in a single step using protein L-Sepharose affinity chromatography. Moreover, human and mouse **monoclonal** IgG, IgM, and IgA, and human IgG Fab fragments, as well as a mouse/human chimeric recombinant antibody, could be purified from cultures of hybridoma cells or antibody-producing bacterial cells, with protein L-Sepharose. This was

also the case with a **humanized** mouse antibody, in which mouse hypervariable antigen-binding regions had been introduced into a protein L-binding kappa subtype III human IgG. These experiments demonstrate that it is possible to engineer antibodies and antibody fragments (Fab, Fv) with protein L-binding framework regions, which can thus be utilized in a protein L-based purification protocol.

DESCRIPTORS:
MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Immune System--Chemical Coordination and Homeostasis
BIOSYSTEMATIC NAMES: **Gram** - **Positive** Cocci--Eubacteria, Bacteria, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: **gram** - **positive** cocci (**Gram** - **Positive** Cocci); human (Hominidae); Muridae (Muridae
COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
MISCELLANEOUS TERMS: ABSTRACT; CORTISOL; IMMUNOGLOBULIN A; IMMUNOGLOBULIN G; IMMUNOGLOBULIN M; LEUKOCYTE; LYMPHOCYTE; MONOCYTE; NEUTROPHIL; PHYSICAL EXERCISE
CONCEPT CODES:
03506 Genetics - Animal
03508 Genetics - Human
10054 Biochemistry methods - Proteins, peptides and amino acids
10504 Biophysics - Methods and techniques
31000 Physiology and biochemistry of bacteria
34502 Immunology - General and methods
BIOSYSTEMATIC CODES:
07700 **Gram** - **Positive** Cocci
86215 Hominidae
86375 Muridae

8/9/16 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008245766 BIOSIS NO.: 199293088657
SPECIFICITY AND PROTECTIVE ACTIVITY OF MURINE MONOCLONAL **ANTIBODIES DIRECTED AGAINST THE CAPSULAR POLYSACCHARIDE OF TYPE III GROUP B STREPTOCOCCI**
AUTHOR: TETI G (Reprint); CALAPAI M; CALOGERO G; TOMASELLO F; MANCUSO G; GALLI A; RIGGIO G
AUTHOR ADDRESS: IST MICROBIOLOGIA, PIAZZA XX SETTEMBRE 4, I-98100 MESSINA, ITALY**ITALY
JOURNAL: Hybridoma 11 (1): p13-22 1992
ISSN: 0272-457X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have obtained 41 **monoclonal** antibodies directed against type III group B streptococci by immunizing Balb/c mice with formalin-killed bacteria. All of these antibodies reacted with purified type-specific carbohydrate by enzyme-linked immunosorbent assay and immunoprecipitation tests. The epitope recognized by all of these antibodies was associated with terminal sialic acid residues, as indicated by abrogation of immune reactions by treatment of the type-specific carbohydrate with neuraminidase. Two purified **monoclonal** antibodies (the IgM P9D8 and the IgG3 P4F12) were further characterized for their protective activity in a neonatal rate model of infection. P9D8 and P4F12 antibodies were significantly protective when administered in a dose of 0.5 and 2.5 mg/kg, respectively, at the same time as 3 .times. 105 colony forming units of type III streptococci. Protection was still observed when the antibodies were given up to 9h after challenge. No protection was afforded against infections with type Ia/c and II streptococci. Similarly, both antibodies effectively opsonized type III, but not Ia, Ib or II bacteria, in an in vitro assay. These and similar, previously

described, **monoclonal** antibodies may be useful, possibly after " **humanization** " by genetic engineering, for the therapy of neonatal group B streptococcal infections.

DESCRIPTORS: HUMAN IMMUNE REACTION IMMUNOGLOBULIN M IMMUNOGLOBULIN G GENETIC ENGINEERING ELISA
DESCRIPTORS:
MAJOR CONCEPTS: Clinical Endocrinology--Human Medicine, Medical Sciences; Genetics; Infection; Pediatrics--Human Medicine, Medical Sciences
BIOSYSTEMATIC NAMES: **Gram** - **Positive** Cocci--Eubacteria, Bacteria, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: Bacteria; Eubacteria; Microorganisms; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
CONCEPT CODES:
03508 Genetics - Human
10064 Biochemistry studies - Proteins, peptides and amino acids
10068 Biochemistry studies - Carbohydrates
12512 Pathology - Therapy
25000 Pediatrics
32600 In vitro cellular and subcellular studies
34508 Immunology - Immunopathology, tissue immunology
36002 Medical and clinical microbiology - Bacteriology
BIOSYSTEMATIC CODES:
07700 **Gram** - **Positive** Cocci
86215 Hominidae
86375 Muridae

8/9/17 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0006982293 BIOSIS NO.: 199039035682
MONOCLONAL **ANTIBODIES AGAINST MICROORGANISMS**
AUTHOR: LEHNER T (Reprint)
AUTHOR ADDRESS: DEP IMMUNOL, UNITED MED DENT SCH GUY'S AND ST THOMAS HOSP, LONDON, UK**UK
JOURNAL: Current Opinion in Immunology 1 (3): p462-466 1989
ISSN: 0952-7915
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: ENGLISH
DESCRIPTORS: REVIEW HUMAN VS. **HUMANIZED** RODENT ANTIBODY HUMAN IMMUNODEFICIENCY VIRUS EPITOPES PNEUMOCYSTIS-CARINII PNEUMONIA DIAGNOSIS STAPHYLOCOCCUS-AUREUS TOXIC SHOCK SYNDROME ANTI-LIPOPOLYSACCHARIDE SCHISTOSOMA-MANSONI STREPTOCOCCUS-MUTANS COLONIZATION PASSIVE IMMUNIZATION
DESCRIPTORS:
MAJOR CONCEPTS: Dental Medicine--Human Medicine, Medical Sciences; Immune System--Chemical Coordination and Homeostasis; Infection; Microbiology; Parasitology; Pharmacology; Pulmonary Medicine--Human Medicine, Medical Sciences; Serology--Allied Medical Sciences; Toxicology
BIOSYSTEMATIC NAMES: Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms; Micrococcaceae-- **Gram** - **Positive** Cocci, Eubacteria, Bacteria, Microorganisms; **Gram** - **Positive** Cocci--Eubacteria, Bacteria, Microorganisms; Sporozoa--Protozoa, Invertebrata, Animalia; Trematoda--Platyhelminthes, Helminthes, Invertebrata, Animalia; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia ; Rodentia--Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: DNA and RNA Reverse Transcribing Viruses; Viruses ; Bacteria; Eubacteria; Microorganisms; Protozoans; Helminths; Invertebrates; Platyhelminths; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates
CONCEPT CODES:
10066 Biochemistry studies - Lipids
10068 Biochemistry studies - Carbohydrates
12504 Pathology - Diagnostic
16006 Respiratory system - Pathology

19006 Dental - Pathology
22005 Pharmacology - Clinical pharmacology
22018 Pharmacology - Immunological processes and allergy
22501 Toxicology - General and methods
22505 Toxicology - Antidotes and prevention
31000 Physiology and biochemistry of bacteria
33506 Virology - Animal host viruses
34502 Immunology - General and methods
34504 Immunology - Bacterial, viral and fungal
35000 Immunology, parasitological
36002 Medical and clinical microbiology - Bacteriology
36006 Medical and clinical microbiology - Virology
36504 Medical and clinical microbiology - Serodiagnosis
60504 Parasitology - Medical
64010 Invertebrata: comparative, experimental morphology, physiology and pathology - Platyhelminthes

BIOSYSTEMATIC CODES:
03305 Retroviridae
07702 Micrococcaceae
07700 **Gram - Positive** Cocci
35400 Sporozoa
45200 Trematoda
86215 Hominidae
86265 Rodentia

8/9/18 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

11123219 EMBASE No: 2001140182

A phase II multicenter study of CAMPATH-1H antibody in previously treated patients with nonbulky non-Hodgkin's lymphoma

Khorana A.; Bunn P.; McLaughlin P.; Vose J.; Stewart C.; Czuczman M.S.
Dr. M.S. Czuczman, Lymphoma Sec. Div. Hematol. Oncol., Bone Marrow Transplantation, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 United States

Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 2001, 41/1-2 (77-87)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 25

CAMPATH-1H is a **humanized** antilymphocyte **monoclonal** antibody (mAb) directed against the CD52 antigen expressed on normal and malignant lymphocytes. We report the results of a multicenter phase II trial using intravenous CAMPATH-1H in previously treated patients with nonbulky non-Hodgkin's lymphoma (NHL) or minimal residual NHL. Sixteen previously treated patients with nonbulky NHL and two patients with minimal residual NHL, were treated with CAMPATH-1H. Changes in peripheral blood lymphocyte subsets were analyzed by multiparameter flow cytometric techniques in eleven patients. The 18 patients enrolled in the studies received CAMPATH-1H for a median duration of 6 weeks (range, 3 to 14 weeks), and a median cumulative dose of 470 mg (range, 180 to 1185 mg). Two of the sixteen patients with nonbulky NHL achieved a complete response (CR) and one patient achieved a partial response (PR). One of the two patients with minimal residual NHL achieved a molecular CR. Infusional complications were seen with the majority of patients but were more common with initial infusions. Significant hematologic toxicity was also observed with grade 3/4 thrombocytopenia (n=10), grade 3/4 neutropenia (n=4) and grade 3 anemia (n=3). Due to excessive infectious complications observed with the patients enrolled, the trials were terminated early. Anti-tumor activity was demonstrated in a small subset of previously treated low-grade lymphoma patients with nonbulky or minimal residual disease. Future studies evaluating the effect of different drug schedules, modes of mAb administration, and concurrent use of prophylactic antibiotics/antiviral/antifungal agents to optimize anti-tumor activity and limit infectious toxicities are planned.

BRAND NAME/MANUFACTURER NAME: cytoxan; ara C; vp 16; novantrone
DRUG DESCRIPTORS:
monoclonal antibody--adverse drug reaction--ae; **monoclonal** antibody --clinical trial--ct; **monoclonal** antibody--drug administration--ad; **monoclonal** antibody--drug dose--do; **monoclonal** antibody--drug therapy --dt; **monoclonal** antibody--pharmacology--pd; **monoclonal** antibody --intravenous drug administration--iv; lymphocyte antibody--adverse drug reaction--ae; lymphocyte antibody--clinical trial--ct; lymphocyte antibody --drug administration--ad; lymphocyte antibody--drug dose--do; lymphocyte antibody--drug therapy--dt; lymphocyte antibody--pharmacology--pd; lymphocyte antibody--intravenous drug administration--iv; CD52 antigen --endogenous compound--ec; antibiotic agent--drug therapy--dt; antivirus agent--drug therapy--dt; antifungal agent--drug therapy--dt; methotrexate --drug combination--cb; methotrexate--drug therapy--dt; bleomycin--drug combination--cb; bleomycin--drug therapy--dt; doxorubicin--drug combination --cb; doxorubicin--drug therapy--dt; cyclophosphamide--drug combination--cb ; cyclophosphamide--drug therapy--dt; vincristine--drug combination--cb; vincristine--drug therapy--dt; dexamethasone--drug combination--cb; dexamethasone--drug therapy--dt; prednisone--drug combination--cb; prednisone--drug therapy--dt; chlorambucil--drug combination--cb; chlorambucil--drug therapy--dt; fludarabine--drug combination--cb; fludarabine--drug therapy--dt; etoposide--drug combination--cb; etoposide --drug therapy--dt; cytarabine--drug combination--cb; cytarabine--drug therapy--dt; lomustine--drug combination--cb; lomustine--drug therapy--dt; ifosfamide--drug combination--cb; ifosfamide--drug therapy--dt; mesna--drug combination--cb; mesna--drug therapy--dt; mitoxantrone--drug combination --cb; mitoxantrone--drug therapy--dt; 5,6 dihydroazacitidine--drug combination--cb; 5,6 dihydroazacitidine--drug therapy--dt; unclassified drug
MEDICAL DESCRIPTORS:
*nonhodgkin lymphoma--drug therapy--dt; *nonhodgkin lymphoma--radiotherapy --rt; *nonhodgkin lymphoma--therapy--th
antigen expression; peripheral lymphocyte; flow cytometry; dose response; treatment outcome; hematologic disease--side effect--si; thrombocytopenia --side effect--si; neutropenia--side effect--si; anemia--side effect--si; disease severity; infection--drug therapy--dt; infection--prevention--pc; infection--side effect--si; antineoplastic activity; antibiotic prophylaxis ; herpes simplex--side effect--si; herpes simplex keratitis--side effect --si; candidiasis--side effect--si; Streptococcus pneumonia--side effect --si; **Staphylococcus** infection--side effect--si; urinary tract infection --side effect--si; Pneumocystis carinii pneumonia--side effect--si; bacterial infection--side effect--si; diarrhea--side effect--si; fever --side effect--si; rash--side effect--si; hypotension--side effect--si; nausea and vomiting--side effect--si; chill--side effect--si; fatigue--side effect--si; hematopoietic stem cell transplantation; human; clinical article; clinical trial; phase 2 clinical trial; multicenter study; aged; adult; article; priority journal
DRUG TERMS (UNCONTROLLED): campath 1h--adverse drug reaction--ae; campath 1h--clinical trial--ct; campath 1h--drug administration--ad; campath 1h --drug dose--do; campath 1h--drug therapy--dt; campath 1h--pharmacology--pd ; campath 1h--intravenous drug administration--iv
CAS REGISTRY NO.: 15475-56-6, 59-05-2, 7413-34-5 (methotrexate); 11056-06-7 (bleomycin); 23214-92-8, 25316-40-9 (doxorubicin); 50-18-0 (cyclophosphamide); 57-22-7 (vincristine); 50-02-2 (dexamethasone); 53-03-2 (prednisone); 305-03-3 (chlorambucil); 21679-14-1 (fludarabine) ; 33419-42-0 (etoposide); 147-94-4, 69-74-9 (cytarabine); 13010-47-4 (lomustine); 3778-73-2 (ifosfamide); 19767-45-4, 3375-50-6 (mesna); 65271-80-9, 70476-82-3 (mitoxantrone); 62402-31-7, 62488-57-7 (5,6 dihydroazacitidine)
SECTION HEADINGS:
016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reaction Titles

8/9/19 (Item 2 from file: 73)

First Hit

L6: Entry 1 of 48 File: PGPB Mar 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040052779 → 10/323926
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040052779 A1

TITLE: Opsonic monoclonal and chimeric antibodies specific for lipoteichoic acid of Gram positive bacteria

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stinson, Jeffrey R.	Brookeville	MD	US	
Schuman, Richard F.	Gaithersburg	MD	US	
Mond, James J.	Silver Spring	MD	US	
Lees, Andrew	Silver Spring	MD	US	
Fischer, Gerald Walter	Bethesda	MD	US	

US-CL-CURRENT: 424/130.1; 530/388.1

CLAIMS:

What is claimed is:

1. A MAb comprising at least one light chain and at least one heavy chain, wherein said at least one light chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said at least one heavy chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12,17, or 22; and wherein said MAb specifically binds to LTA.

2. The Mab according to claim 1, wherein the percents identity are at least 80%.

3. The Mab according to claim 1, wherein the percents identity are at least 90%.

4. The MAb of claim 1, comprising at least one variable region having an amino acid sequence selected from Seq. ID Nos. 10, 12, 16, 17, 21, and 22.

5. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both are chimeric or humanized.

6. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both, are human.

7. The MAb according to claim 1, comprising a heavy chain constant region; wherein said constant region comprises human IgG, IgA, IgM, or IgD sequence.

8. The MAb of claim 1, comprising a Fab, Fab', F(ab').sub.2, Fv, SFv, scFv.

9. A polypeptide comprising an amino acid sequence having at least 70% identity with with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

10. The polypeptide according to claim 9, comprising at least one region having at least 88% identity with a sequence selected from amino acids 24-33, 49-55, and 88-73 of Seq. ID Nos. 10,16, or 21; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

11. The polypeptide according to claim 9, comprising at least one region having at least 82% identity with a sequence selected from amino acids amino acids 1-23, 34-38, 56-87, and 97-106 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

12. A MAb light chain comprising the polypeptide according to claim 9.

13. The Mab light chain according to claim 12, wherein said light chain is chimeric, humanized, or human.

14. The MAb light chain according to claim 12, comprising a light chain constant region comprising human kappa or lambda sequence.

15. A polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; wherein wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

16. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids 26-35, and 50-69 of Seq. ID Nos. 12,17, or 22; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

17. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids amino acids 1-25, 36-49, 70-101, and 115-125 Seq. ID Nos. 12,17, or 22; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

18. A MAb heavy chain comprising the polypeptide according to claim 15.

19. The Mab heavy chain according to claim 18, wherein said heavy chain is chimeric, humanized, or human.

20. The MAb heavy chain according to claim 18, comprising a heavy chain constant region comprising human IgG, IgA, IgM, or IgD sequence.

21. A MAb comprising at least one light chain and at least one heavy chain, wherein said MAb specifically binds LTA; and wherein said at least one light chain comprises comprises a variable region having at least one CDR comprising a sequence selected from amino acids 24-33, 49-55, or 88-73 of Seq. ID Nos. 10, 16, or 21; or wherein said at least one light chain comprises a variable region having at least one CDR comprising a sequence selected from amino acids 1-25, 36-49, 70-101, or 115-125 of Seq. ID Nos. 12,17, or 22.

22. A Mab according to claim 21, comprising at least one variable domain selected from A110, A110b, A120, A120b, and 391.4.

23. A hybridoma cell line expressing a MAb according to claim 22.

24. A pharmaceutical composition comprising one or more Mabs according to claim 1 and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition according to claim 24, wherein said composition is opsonic for S. epidermidis and S. aureus.

26. The pharmaceutical composition of claim 25, further comprising at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

27. A method of treating a patient comprising administering the pharmaceutical composition of claim 24.

28. The method of claim 27, wherein the composition is administered internasally.

29. The method of claim 27, wherein the pharmaceutical composition further comprises at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

30. The method of claim 29, wherein the composition is administered internasally.

31. A method of making the MAb of claim 1 comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the the light chain variable region of said at least one Mab; c) selecting a polypeptide polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16,10, and 21; d) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; e) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12,17, or 22; f) combining a light chain comprising a polypeptide sequence of step c) with a heavy chain comprising a polypeptide sequence of step e).

32. A method of making the polypeptide of claim 9, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the light chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21.

33. A method of making the polypeptide of claim 15, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22.

34. A purified nucleic acid encoding the polypeptide of claim 9.

35. A purified nucleic acid encoding the polypeptide of claim 15.

36. A production system comprising, 1) a cell; and 2) one or more recombinant

nucleic acids capable of directing the expression of a Mab according to claim 1.

37. A method of identifying highly antigenic and highly conserved epitopes comprising the steps of: a) selecting a multiplicity of MAbs that specifically binds binds to an immunogen; b) determining the polypeptide sequence of the variable regions of said MAbs; d) identifying regions of identity in the polypeptide sequence sequence of at least two of said Mabs, said regions of identity comprising at least one of 1) at least 70% identity of light chain variable regions, at least 70% identity of heavy chain variable regions, at least 70% identity over 3 complementarity determining regions (CDRs) in a variable region, at least 75% identity over at least two CDRs in a variable region; at least 80% identity in a CDR; and at least 70% identity in the framework regions (FRs) of a variable region.

38. A collection of Mabs that bind to LTA comprising, a multiplicity of Mabs according to claim 1.

39. The collection of claim 38, wherein the collection comprises one or more of M110, M120, 391.4, or a chimeric or humanized derivative thereof.

First Hit

Generate Collection Print

L6: Entry 8 of 48 File: PGPB Dec 25, 2003

PGPUB-DOCUMENT-NUMBER: 20030235578 ⇒ 10/323,927
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030235578 A1

TITLE: Opsonic monoclonal and chimeric antibodies specific for lipoteichoic acid of Gram positive bacteria

PUBLICATION-DATE: December 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stinson, Jeffrey R.	Brookeville	MD	US	
Schuman, Richard F.	Gaithersburg	MD	US	
Mond, James J.	Silver Spring	MD	US	
Lees, Andrew	Silver Spring	MD	US	
Fischer, Gerald Walter	Bethesda	MD	US	

US-CL-CURRENT: 424/130.1; 530/387.1, 530/388.15

CLAIMS:

What is claimed is:

1. A MAb comprising at least one light chain and at least one heavy chain, wherein said at least one light chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said at least one heavy chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; and wherein said MAb specifically binds to LTA.

2. The Mab according to claim 1, wherein the percents identity are at least 80%.

3. The Mab according to claim 1, wherein the percents identity are at least 90%.

4. The MAb of claim 1, comprising at least one variable region having an amino acid sequence selected from Seq. ID Nos. 10, 12, 16, 17, 21, and 22.

5. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both are chimeric or humanized.

6. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both, are human.

7. The MAb according to claim 1, comprising a heavy chain constant region; wherein said constant region comprises human IgG, IgA, IgM, or IgD sequence.

8. The MAb of claim 1, comprising a Fab, Fab', F(ab').sub.2, Fv, SFv, scFv.

9. A polypeptide comprising an amino acid sequence having at least 70% identity with with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

10. The polypeptide according to claim 9, comprising at least one region having at least 88% identity with a sequence selected from amino acids 24-33, 49-55, and 88-73 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

11. The polypeptide according to claim 9, comprising at least one region having at least 82% identity with a sequence selected from amino acids amino acids 1-23, 34-38, 56-87, and 97-106 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

12. A MAb light chain comprising the polypeptide according to claim 9.

13. The Mab light chain according to claim 12, wherein said light chain is chimeric, humanized, or human.

14. The MAb light chain according to claim 12, comprising a light chain constant region comprising human kappa or lambda sequence.

15. A polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; wherein wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

16. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids 26-35, and 50-69 of Seq. ID Nos. 12, 17, or 22; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

17. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids amino acids 1-25, 36-49, 70-101, and 115-125 Seq. ID Nos. 12, 17, or 22; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

18. A MAb heavy chain comprising the polypeptide according to claim 15.

19. The Mab heavy chain according to claim 18, wherein said heavy chain is chimeric, humanized, or human.

20. The MAb heavy chain according to claim 18, comprising a heavy chain constant region comprising human IgG, IgA, IgM, or IgD sequence.

21. A MAb comprising at least one light chain and at least one heavy chain, wherein said MAb specifically binds LTA; and wherein said at least one light chain comprises comprises a variable region having at least one CDR comprising a sequence selected from amino acids 24-33, 49-55, or 88-73 of Seq. ID Nos. 10, 16, or 21; or wherein said at least one light chain comprises a variable region having at least one CDR comprising a sequence selected from amino acids 1-25, 36-49, 70-101, or 115-125 of Seq. ID Nos. 12, 17, or 22.

22. A Mab according to claim 21, comprising at least one variable domain selected from A110, A110b, A120, A120b, and 391.4.

23. A hybridoma cell line expressing a MAb according to claim 22.

24. A pharmaceutical composition comprising one or more Mabs according to claim 1 and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition according to claim 24, wherein said composition is opsonic for S. epidermidis and S. aureus.

26. The pharmaceutical composition of claim 25, further comprising at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

27. A method of treating a patient comprising administering the pharmaceutical composition of claim 24.

28. The method of claim 27, wherein the composition is administered internasally.

29. The method of claim 27, wherein the pharmaceutical composition further comprises at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

30. The method of claim 29, wherein the composition is administered internasally.

31. A method of making the MAb of claim 1 comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the the light chain variable region of said at least one Mab; c) selecting a polypeptide polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; d) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; e) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; f) combining a light chain comprising a polypeptide sequence of step c) with a heavy chain comprising a polypeptide sequence of step e).

32. A method of making the polypeptide of claim 9, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the light chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21.

33. A method of making the polypeptide of claim 15, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22.

34. A purified nucleic acid encoding the polypeptide of claim 9.

35. A purified nucleic acid encoding the polypeptide of claim 15.

36. A production system comprising, 1) a cell; and 2) one or more recombinant

nucleic acids capable of directing the expression of a Mab according to claim 1.

37. A method of identifying highly antigenic and highly conserved epitopes comprising the steps of: a) selecting a multiplicity of MAbs that specifically binds binds to an immunogen; b) determining the polypeptide sequence of the variable regions of said MAbs; d) identifying regions of identity in the polypeptide sequence sequence of at least two of said Mabs, said regions of identity comprising at least one of 1) at least 70% identity of light chain variable regions, at least 70% identity of heavy chain variable regions, at least 70% identity over 3 complementarity determining regions (CDRs) in a variable region, at least 75% identity over at least two CDRs in a variable region; at least 80% identity in a CDR; and at least 70% identity in the framework regions (FRs) of a variable region.

38. A collection of Mabs that bind to LTA comprising, a multiplicity of Mabs according to claim 1.

39. The collection of claim 38, wherein the collection comprises one or more of M110, M120, 391.4, or a chimeric or humanized derivative thereof.

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L6: Entry 7 of 48 File: PGPB Jan 22, 2004

PGPUB-DOCUMENT-NUMBER: 20040013673 10/601171
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040013673 A1

TITLE: Opsonic and protective monoclonal and chimeric antibodies specific for lipoteichoic acid of gram posiive bacteria

PUBLICATION-DATE: January 22, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Schuman, Richard F.	Gaithersburg	MD	US	
Wong, Hing	Weston	FL	US	
Stinson, Jeffrey R.	Davie	FL	US	

US-CL-CURRENT: 424/164.1; 530/388.4, 536/53

CLAIMS:

We claim:

1. A monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the the monoclonal antibody (a) binds to lipoteichoic acid at a level that is twice background or greater and (b) enhances the opsonization of Gram positive bacteria by 75% or more.

2. The monoclonal antibody of claim 1 wherein the antibody binds a peptide sequence selected from the group consisting of:

13 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

3. The monoclonal antibody of claim 1 wherein the antibody is a chimeric non-human/human antibody.

4. The chimeric antibody of claim 3 comprising at least part of a human immunoglobulin constant region and-at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

5. A chimeric immunoglobulin chain comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

6. The chimeric immunoglobulin chain of claim 5 wherein the constant region is selected from the group consisting of IgG, IgA, and IgM.

7. The chimeric immunoglobulin chain of claim 5 wherein the chain is selected from the group consisting of a heavy chain and a light chain.

8. The chimeric immunoglobulin chain of claim 7 wherein the chain is a light chain is selected from the group consisting of a kappa chain and a lambda chain.

9. An antibody to lipoteichoic acid of Gram positive bacteria wherein the antibody (a) binds to lipoteichoic acid at a level that is twice background or greater; (b) enhances the opsonization of Gram positive bacteria by 75% or more; and (c) binds to a peptide sequence selected from the group consisting of:

14 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

10. A pharmaceutical composition comprising the antibody of one of claims 1 or 9, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

11. A protective monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the antibody enhances survival in a lethal animal model by 10% or more.

12. The protective monoclonal antibody of claim 11, wherein the antibody binds to a peptide sequence selected from the group consisting of:

15 W R M Y F S H R H A H L R S P and (SEQ ID NO:1) W H W R H R I P L Q L A A G R. (SEQ ID NO:2)

13. A pharmaceutical composition comprising the antibody of claim 11, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

14. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 10 or 13.

15. A method for preventing infections caused by Gram positive infections in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 10 or 13.

16. An lipoteichoic acid epitope peptide mimic comprising a peptide sequence selected from the group consisting of:

16 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

17. A peptide encoded by the DNA of the variable region of the anti-lipoteichoic antibody of FIG. 12 or a sequence that is at least 70% homologous to that DNA.

18. The peptide of claim 17 wherein the variable region on a chain is selected from the group consisting of the heavy chain and light chain.

19. The peptide of claim 17 wherein the DNA of the variable region encodes one or more of the Complementarity Determining Regions.

20. The peptide of claim 19 wherein the variable region is on a chain selected from

the group consisting of the heavy chain and light chain.

21. A peptide characterized by amino acids corresponding to one or more of the Complementarity Determining Regions of the variable region of the anti-lipoteichoic antibody of FIG. 12 or amino acids that are at least 70% homologous to the Complementarity Determining Regions.

22. The peptide of claim 21 wherein the variable region is selected from the group consisting of the heavy chain and the light chain.

23. A pharmaceutical composition comprising the peptides of any of claims 16-22 and a pharmaceutically acceptable carrier.

24. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 23.

25. A method for preventing infections caused by Gram positive bacteria in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 23.

26. A vaccine for preventing infections caused by Gram positive bacteria comprising a lipoteichoic acid antigen and a pharmaceutically acceptable carrier.

27. The vaccine of claim 26 wherein the lipoteichoic acid antigen comprises the epitope of the antigen or an epitope mimic.

28. The vaccine of claim 26 wherein the epitope is a peptide sequence selected from the group consisting of:

17 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

29. An animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by Gram positive bacteria comprising the steps of: a) administering a lipid emulsion to at least two groups of suckling rodents; b) injecting into one group the composition to be tested and injecting into the other group a control substance; c) administering through a catheter an amount of Gram positive bacteria sufficient to cause lethal sepsis; d) leaving the catheter under the skin of the rodent; and d) assessing the affect of administration of the composition on either or both bacteremia and survival, wherein compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by Gram positive bacteria.

30. The method of claim 29 wherein the composition to be tested is an antibody to lipoteichoic acid of Gram positive bacteria or fragments thereof.

31. The method of claim 29 wherein the Gram positive bacteria is selected from the group consisting of Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus hominus, Staphylococcus aureus, Staphylococcus mutans, Staphylococcus faecalis, and Staphylococcus pyogenes.

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L6: Entry 7 of 48 File: PGPB Jan 22, 2004

PGPUB-DOCUMENT-NUMBER: 20040013673
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040013673 A1

TITLE: Opsonic and protective monoclonal and chimeric antibodies specific for lipoteichoic acid of gram posiive bacteria

PUBLICATION-DATE: January 22, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Wong, Hing	Weston	FL	US	
Stinson, Jeffrey R.	Davie	FL	US	

US-CL-CURRENT: 424/164.1; 530/388.4, 536/53

CLAIMS:

We claim:

1. A monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the the monoclonal antibody (a) binds to lipoteichoic acid at a level that is twice background or greater and (b) enhances the opsonization of Gram positive bacteria by 75% or more.

2. The monoclonal antibody of claim 1 wherein the antibody binds a peptide sequence selected from the group consisting of:

13 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

3. The monoclonal antibody of claim 1 wherein the antibody is a chimeric non-human/human antibody.

4. The chimeric antibody of claim 3 comprising at least part of a human immunoglobulin constant region and-at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

5. A chimeric immunoglobulin chain comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

6. The chimeric immunoglobulin chain of claim 5 wherein the constant region is selected from the group consisting of IgG, IgA, and IgM.

7. The chimeric immunoglobulin chain of claim 5 wherein the chain is selected from the group consisting of a heavy chain and a light chain.

8. The chimeric immunoglobulin chain of claim 7 wherein the chain is a light chain is selected from the group consisting of a kappa chain and a lambda chain.

9. An antibody to lipoteichoic acid of Gram positive bacteria wherein the antibody (a) binds to lipoteichoic acid at a level that is twice background or greater; (b) enhances the opsonization of Gram positive bacteria by 75% or more; and (c) binds to a peptide sequence selected from the group consisting of:

14 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

10. A pharmaceutical composition comprising the antibody of one of claims 1 or 9, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

11. A protective monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the antibody enhances survival in a lethal animal model by 10% or more.

12. The protective monoclonal antibody of claim 11, wherein the antibody binds to a peptide sequence selected from the group consisting of:

15 W R M Y F S H R H A H L R S P and (SEQ ID NO:1) W H W R H R I P L Q L A A G R. (SEQ ID NO:2)

13. A pharmaceutical composition comprising the antibody of claim 11, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

14. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 10 or 13.

15. A method for preventing infections caused by Gram positive infections in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 10 or 13.

16. An lipoteichoic acid epitope peptide mimic comprising a peptide sequence selected from the group consisting of:

16 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

17. A peptide encoded by the DNA of the variable region of the anti-lipoteichoic antibody of FIG. 12 or a sequence that is at least 70% homologous to that DNA.

18. The peptide of claim 17 wherein the variable region on a chain is selected from the group consisting of the heavy chain and light chain.

19. The peptide of claim 17 wherein the DNA of the variable region encodes one or more of the Complementarity Determining Regions.

20. The peptide of claim 19 wherein the variable region is on a chain selected from

the group consisting of the heavy chain and light chain.

21. A peptide characterized by amino acids corresponding to one or more of the Complementarity Determining Regions of the variable region of the anti-lipoteichoic antibody of FIG. 12 or amino acids that are at least 70% homologous to the Complementarity Determining Regions.

22. The peptide of claim 21 wherein the variable region is selected from the group consisting of the heavy chain and the light chain.

23. A pharmaceutical composition comprising the peptides of any of claims 16-22 and a pharmaceutically acceptable carrier.

24. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 23.

25. A method for preventing infections caused by Gram positive bacteria in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 23.

26. A vaccine for preventing infections caused by Gram positive bacteria comprising a lipoteichoic acid antigen and a pharmaceutically acceptable carrier.

27. The vaccine of claim 26 wherein the lipoteichoic acid antigen comprises the epitope of the antigen or an epitope mimic.

28. The vaccine of claim 26 wherein the epitope is a peptide sequence selected from the group consisting of:

17 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

29. An animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by Gram positive bacteria comprising the steps of: a) administering a lipid emulsion to at least two groups of suckling rodents; b) injecting into one group the composition to be tested and injecting into the other group a control substance; c) administering through a catheter an amount of Gram positive bacteria sufficient to cause lethal sepsis; d) leaving the catheter under the skin of the rodent; and d) assessing the affect of administration of the composition on either or both bacteremia and survival, wherein compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by Gram positive bacteria.

30. The method of claim 29 wherein the composition to be tested is an antibody to lipoteichoic acid of Gram positive bacteria or fragments thereof.

31. The method of claim 29 wherein the Gram positive bacteria is selected from the group consisting of Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus hominus, Staphylococcus aureus, Staphylococcus mutans, Staphylococcus faecalis, and Staphylococcus pyogenes.

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L6: Entry 1 of 48 File: PGPB Mar 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040052779 → 10/323926
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040052779 A1

TITLE: Opsonic monoclonal and chimeric antibodies specific for lipoteichoic acid of Gram positive bacteria

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stinson, Jeffrey R.	Brookeville	MD	US	
Schuman, Richard F.	Gaithersburg	MD	US	
Mond, James J.	Silver Spring	MD	US	
Lees, Andrew	Silver Spring	MD	US	
Fischer, Gerald Walter	Bethesda	MD	US	

US-CL-CURRENT: 424/130.1; 530/388.1

CLAIMS:

What is claimed is:

1. A MAb comprising at least one light chain and at least one heavy chain, wherein said at least one light chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said at least one heavy chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12,17, or 22; and wherein said MAb specifically binds to LTA.

2. The Mab according to claim 1, wherein the percents identity are at least 80%.

3. The Mab according to claim 1, wherein the percents identity are at least 90%.

4. The MAb of claim 1, comprising at least one variable region having an amino acid sequence selected from Seq. ID Nos. 10, 12, 16, 17, 21, and 22.

5. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both are chimeric or humanized.

6. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both, are human.

7. The MAb according to claim 1, comprising a heavy chain constant region; wherein said constant region comprises human IgG, IgA, IgM, or IgD sequence.

8. The MAb of claim 1, comprising a Fab, Fab', F(ab').sub.2, Fv, SFv, scFv.

9. A polypeptide comprising an amino acid sequence having at least 70% identity with with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

10. The polypeptide according to claim 9, comprising at least one region having at least 88% identity with a sequence selected from amino acids 24-33, 49-55, and 88-73 of Seq. ID Nos. 10,16, or 21; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

11. The polypeptide according to claim 9, comprising at least one region having at least 82% identity with a sequence selected from amino acids amino acids 1-23, 34-38, 56-87, and 97-106 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

12. A MAb light chain comprising the polypeptide according to claim 9.

13. The Mab light chain according to claim 12, wherein said light chain is chimeric, humanized, or human.

14. The MAb light chain according to claim 12, comprising a light chain constant region comprising human kappa or lambda sequence.

15. A polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; wherein wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

16. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids 26-35, and 50-69 of Seq. ID Nos. 12,17, or 22; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

17. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids amino acids 1-25, 36-49, 70-101, and 115-125 Seq. ID Nos. 12,17, or 22; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

18. A MAb heavy chain comprising the polypeptide according to claim 15.

19. The Mab heavy chain according to claim 18, wherein said heavy chain is chimeric, humanized, or human.

20. The MAb heavy chain according to claim 18, comprising a heavy chain constant region comprising human IgG, IgA, IgM, or IgD sequence.

21. A MAb comprising at least one light chain and at least one heavy chain, wherein said MAb specifically binds LTA; and wherein said at least one light chain comprises comprises a variable region having at least one CDR comprising a sequence selected from amino acids 24-33, 49-55, or 88-73 of Seq. ID Nos. 10, 16, or 21; or wherein said at least one light chain comprises a variable region having at least one CDR comprising a sequence selected from amino acids 1-25, 36-49, 70-101, or 115-125 of Seq. ID Nos. 12,17, or 22.

22. A Mab according to claim 21, comprising at least one variable domain selected from A110, A110b, A120, A120b, and 391.4.

23. A hybridoma cell line expressing a MAb according to claim 22.

24. A pharmaceutical composition comprising one or more Mabs according to claim 1 and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition according to claim 24, wherein said composition is opsonic for S. epidermidis and S. aureus.

26. The pharmaceutical composition of claim 25, further comprising at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

27. A method of treating a patient comprising administering the pharmaceutical composition of claim 24.

28. The method of claim 27, wherein the composition is administered internasally.

29. The method of claim 27, wherein the pharmaceutical composition further comprises at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

30. The method of claim 29, wherein the composition is administered internasally.

31. A method of making the MAb of claim 1 comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the the light chain variable region of said at least one Mab; c) selecting a polypeptide polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16,10, and 21; d) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; e) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12,17, or 22; f) combining a light chain comprising a polypeptide sequence of step c) with a heavy chain comprising a polypeptide sequence of step e).

32. A method of making the polypeptide of claim 9, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the light chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21.

33. A method of making the polypeptide of claim 15, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22.

34. A purified nucleic acid encoding the polypeptide of claim 9.

35. A purified nucleic acid encoding the polypeptide of claim 15.

36. A production system comprising, 1) a cell; and 2) one or more recombinant

nucleic acids capable of directing the expression of a Mab according to claim 1.

37. A method of identifying highly antigenic and highly conserved epitopes comprising the steps of: a) selecting a multiplicity of MAbs that specifically binds binds to an immunogen; b) determining the polypeptide sequence of the variable regions of said MAbs; d) identifying regions of identity in the polypeptide sequence sequence of at least two of said Mabs, said regions of identity comprising at least one of 1) at least 70% identity of light chain variable regions, at least 70% identity of heavy chain variable regions, at least 70% identity over 3 complementarity determining regions (CDRs) in a variable region, at least 75% identity over at least two CDRs in a variable region; at least 80% identity in a CDR; and at least 70% identity in the framework regions (FRs) of a variable region.

38. A collection of Mabs that bind to LTA comprising, a multiplicity of Mabs according to claim 1.

39. The collection of claim 38, wherein the collection comprises one or more of M110, M120, 391.4, or a chimeric or humanized derivative thereof.

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L6: Entry 8 of 48 File: PGPB Dec 25, 2003

10/323,927

PGPUB-DOCUMENT-NUMBER: 20030235578
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030235578 A1

TITLE: Opsonic monoclonal and chimeric antibodies specific for lipoteichoic acid of Gram positive bacteria

PUBLICATION-DATE: December 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stinson, Jeffrey R.	Brookeville	MD	US	
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Mond, James J.	Silver Spring	MD	US	
Lees, Andrew	Silver Spring	MD	US	
Fischer, Gerald Walter	Bethesda	MD	US	

US-CL-CURRENT: 424/130.1; 530/387.1, 530/388.15

CLAIMS:

What is claimed is:

1. A MAb comprising at least one light chain and at least one heavy chain, wherein said at least one light chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said at least one heavy chain comprises a polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; and wherein said MAb specifically binds to LTA.

2. The Mab according to claim 1, wherein the percents identity are at least 80%.

3. The Mab according to claim 1, wherein the percents identity are at least 90%.

4. The MAb of claim 1, comprising at least one variable region having an amino acid sequence selected from Seq. ID Nos. 10, 12, 16, 17, 21, and 22.

5. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both are chimeric or humanized.

6. The MAb according to claim 1, wherein at least one light chain, at least one heavy chain, or both, are human.

7. The MAb according to claim 1, comprising a heavy chain constant region; wherein said constant region comprises human IgG, IgA, IgM, or IgD sequence.

8. The MAb of claim 1, comprising a Fab, Fab', F(ab').sub.2, Fv, SFv, scFv.

9. A polypeptide comprising an amino acid sequence having at least 70% identity with with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

10. The polypeptide according to claim 9, comprising at least one region having at least 88% identity with a sequence selected from amino acids 24-33, 49-55, and 88-73 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

11. The polypeptide according to claim 9, comprising at least one region having at least 82% identity with a sequence selected from amino acids amino acids 1-23, 34-38, 56-87, and 97-106 of Seq. ID Nos. 10, 16, or 21; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

12. A MAb light chain comprising the polypeptide according to claim 9.

13. The Mab light chain according to claim 12, wherein said light chain is chimeric, humanized, or human.

14. The MAb light chain according to claim 12, comprising a light chain constant region comprising human kappa or lambda sequence.

15. A polypeptide comprising an amino acid sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; wherein wherein said polypeptide is capable of functioning as a variable region, or portion thereof, in a MAb that specifically binds to LTA.

16. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids 26-35, and 50-69 of Seq. ID Nos. 12, 17, or 22; wherein said region is capable of functioning as a CDR, or portion thereof, in a MAb that specifically binds to LTA.

17. The polypeptide according to claim 15, comprising at least one region having at least 80% identity with a sequence selected from amino acids amino acids 1-25, 36-49, 70-101, and 115-125 Seq. ID Nos. 12, 17, or 22; wherein said region is capable of functioning as a framework region, or portion thereof, in a MAb that specifically specifically binds to LTA.

18. A MAb heavy chain comprising the polypeptide according to claim 15.

19. The Mab heavy chain according to claim 18, wherein said heavy chain is chimeric, humanized, or human.

20. The MAb heavy chain according to claim 18, comprising a heavy chain constant region comprising human IgG, IgA, IgM, or IgD sequence.

21. A MAb comprising at least one light chain and at least one heavy chain, wherein said MAb specifically binds LTA; and wherein said at least one light chain comprises comprises a variable region having at least one CDR comprising a sequence selected from amino acids 24-33, 49-55, or 88-73 of Seq. ID Nos. 10, 16, or 21; or wherein said at least one light chain comprises a variable region having at least one CDR comprising a sequence selected from amino acids 1-25, 36-49, 70-101, or 115-125 of Seq. ID Nos. 12, 17, or 22.

22. A Mab according to claim 21, comprising at least one variable domain selected from A110, A110b, A120, A120b, and 391.4.

23. A hybridoma cell line expressing a MAb according to claim 22.

24. A pharmaceutical composition comprising one or more Mabs according to claim 1 and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition according to claim 24, wherein said composition is opsonic for S. epidermidis and S. aureus.

26. The pharmaceutical composition of claim 25, further comprising at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

27. A method of treating a patient comprising administering the pharmaceutical composition of claim 24.

28. The method of claim 27, wherein the composition is administered internasally.

29. The method of claim 27, wherein the pharmaceutical composition further comprises at least one antibody that binds to peptidoglycan (PepG) of Gram-positive bacteria.

30. The method of claim 29, wherein the composition is administered internasally.

31. A method of making the MAb of claim 1 comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the the light chain variable region of said at least one Mab; c) selecting a polypeptide polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21; d) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; e) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22; f) combining a light chain comprising a polypeptide sequence of step c) with a heavy chain comprising a polypeptide sequence of step e).

32. A method of making the polypeptide of claim 9, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the light chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a light chain variable region selected from Seq. ID Nos. 16, 10, and 21.

33. A method of making the polypeptide of claim 15, comprising the steps of: a) selecting at least one Mab that specifically binds to at least of LTA, or a peptide mimeotope of LTA that induces anti-LTA antibodies; b) determining the polypeptide sequence of the heavy chain variable region of said at least one Mab; d) selecting a a polypeptide sequence having at least 70% identity with a heavy chain variable region selected from Seq. ID Nos. 12, 17, or 22.

34. A purified nucleic acid encoding the polypeptide of claim 9.

35. A purified nucleic acid encoding the polypeptide of claim 15.

36. A production system comprising, 1) a cell; and 2) one or more recombinant

nucleic acids capable of directing the expression of a Mab according to claim 1.

37. A method of identifying highly antigenic and highly conserved epitopes comprising the steps of: a) selecting a multiplicity of MAbs that specifically binds binds to an immunogen; b) determining the polypeptide sequence of the variable regions of said MAbs; d) identifying regions of identity in the polypeptide sequence sequence of at least two of said Mabs, said regions of identity comprising at least one of 1) at least 70% identity of light chain variable regions, at least 70% identity of heavy chain variable regions, at least 70% identity over 3 complementarity determining regions (CDRs) in a variable region, at least 75% identity over at least two CDRs in a variable region; at least 80% identity in a CDR; and at least 70% identity in the framework regions (FRs) of a variable region.

38. A collection of Mabs that bind to LTA comprising, a multiplicity of Mabs according to claim 1.

39. The collection of claim 38, wherein the collection comprises one or more of M110, M120, 391.4, or a chimeric or humanized derivative thereof.

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L6: Entry 7 of 48 File: PGPB Jan 22, 2004

PGPUB-DOCUMENT-NUMBER: 20040013673 10/601171
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TITLE: Opsonic and protective monoclonal and chimeric antibodies specific for lipoteichoic acid of gram posiive bacteria

PUBLICATION-DATE: January 22, 2004

INVENTOR-INFORMATION:

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Wong, Hing	Weston	FL	US	
Stinson, Jeffrey R.	Davie	FL	US	

US-CL-CURRENT: 424/164.1; 530/388.4, 536/53

CLAIMS:

We claim:

1. A monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the the monoclonal antibody (a) binds to lipoteichoic acid at a level that is twice background or greater and (b) enhances the opsonization of Gram positive bacteria by 75% or more.

2. The monoclonal antibody of claim 1 wherein the antibody binds a peptide sequence selected from the group consisting of:

13 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

3. The monoclonal antibody of claim 1 wherein the antibody is a chimeric non-human/human antibody.

4. The chimeric antibody of claim 3 comprising at least part of a human immunoglobulin constant region and-at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

5. A chimeric immunoglobulin chain comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

6. The chimeric immunoglobulin chain of claim 5 wherein the constant region is selected from the group consisting of IgG, IgA, and IgM.

7. The chimeric immunoglobulin chain of claim 5 wherein the chain is selected from the group consisting of a heavy chain and a light chain.

8. The chimeric immunoglobulin chain of claim 7 wherein the chain is a light chain is selected from the group consisting of a kappa chain and a lambda chain.

9. An antibody to lipoteichoic acid of Gram positive bacteria wherein the antibody (a) binds to lipoteichoic acid at a level that is twice background or greater; (b) enhances the opsonization of Gram positive bacteria by 75% or more; and (c) binds to a peptide sequence selected from the group consisting of:

14 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

10. A pharmaceutical composition comprising the antibody of one of claims 1 or 9, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

11. A protective monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the antibody enhances survival in a lethal animal model by 10% or more.

12. The protective monoclonal antibody of claim 11, wherein the antibody binds to a peptide sequence selected from the group consisting of:

15 W R M Y F S H R H A H L R S P and (SEQ ID NO:1) W H W R H R I P L Q L A A G R. (SEQ ID NO:2)

13. A pharmaceutical composition comprising the antibody of claim 11, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

14. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 10 or 13.

15. A method for preventing infections caused by Gram positive infections in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 10 or 13.

16. An lipoteichoic acid epitope peptide mimic comprising a peptide sequence selected from the group consisting of:

16 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

17. A peptide encoded by the DNA of the variable region of the anti-lipoteichoic antibody of FIG. 12 or a sequence that is at least 70% homologous to that DNA.

18. The peptide of claim 17 wherein the variable region on a chain is selected from the group consisting of the heavy chain and light chain.

19. The peptide of claim 17 wherein the DNA of the variable region encodes one or more of the Complementarity Determining Regions.

20. The peptide of claim 19 wherein the variable region is on a chain selected from

the group consisting of the heavy chain and light chain.

21. A peptide characterized by amino acids corresponding to one or more of the Complementarity Determining Regions of the variable region of the anti-lipoteichoic antibody of FIG. 12 or amino acids that are at least 70% homologous to the Complementarity Determining Regions.

22. The peptide of claim 21 wherein the variable region is selected from the group consisting of the heavy chain and the light chain.

23. A pharmaceutical composition comprising the peptides of any of claims 16-22 and a pharmaceutically acceptable carrier.

24. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 23.

25. A method for preventing infections caused by Gram positive bacteria in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 23.

26. A vaccine for preventing infections caused by Gram positive bacteria comprising a lipoteichoic acid antigen and a pharmaceutically acceptable carrier.

27. The vaccine of claim 26 wherein the lipoteichoic acid antigen comprises the epitope of the antigen or an epitope mimic.

28. The vaccine of claim 26 wherein the epitope is a peptide sequence selected from the group consisting of:

17 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

29. An animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by Gram positive bacteria comprising the steps of: a) administering a lipid emulsion to at least two groups of suckling rodents; b) injecting into one group the composition to be tested and injecting into the other group a control substance; c) administering through a catheter an amount of Gram positive bacteria sufficient to cause lethal sepsis; d) leaving the catheter under the skin of the rodent; and d) assessing the affect of administration of the composition on either or both bacteremia and survival, wherein compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by Gram positive bacteria.

30. The method of claim 29 wherein the composition to be tested is an antibody to lipoteichoic acid of Gram positive bacteria or fragments thereof.

31. The method of claim 29 wherein the Gram positive bacteria is selected from the group consisting of Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus hominus, Staphylococcus aureus, Staphylococcus mutans, Staphylococcus faecalis, and Staphylococcus pyogenes.

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L6: Entry 7 of 48 File: PGPB Jan 22, 2004

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PUBLICATION-DATE: January 22, 2004

INVENTOR-INFORMATION:

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Schuman, Richard F.	Gaithersburg	MD	US	
Wong, Hing	Weston	FL	US	
Stinson, Jeffrey R.	Davie	FL	US	

US-CL-CURRENT: 424/164.1; 530/388.4, 536/53

CLAIMS:

We claim:

1. A monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the the monoclonal antibody (a) binds to lipoteichoic acid at a level that is twice background or greater and (b) enhances the opsonization of Gram positive bacteria by 75% or more.

2. The monoclonal antibody of claim 1 wherein the antibody binds a peptide sequence selected from the group consisting of:

13 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

3. The monoclonal antibody of claim 1 wherein the antibody is a chimeric non-human/human antibody.

4. The chimeric antibody of claim 3 comprising at least part of a human immunoglobulin constant region and-at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

5. A chimeric immunoglobulin chain comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to lipoteichoic acid of Gram positive bacteria.

6. The chimeric immunoglobulin chain of claim 5 wherein the constant region is selected from the group consisting of IgG, IgA, and IgM.

7. The chimeric immunoglobulin chain of claim 5 wherein the chain is selected from the group consisting of a heavy chain and a light chain.

8. The chimeric immunoglobulin chain of claim 7 wherein the chain is a light chain is selected from the group consisting of a kappa chain and a lambda chain.

9. An antibody to lipoteichoic acid of Gram positive bacteria wherein the antibody (a) binds to lipoteichoic acid at a level that is twice background or greater; (b) enhances the opsonization of Gram positive bacteria by 75% or more; and (c) binds to a peptide sequence selected from the group consisting of:

14 W R M Y F S H R H A H L R S P and (SEQ ID NO 1) W H W R H R I P L Q L A A G R. (SEQ ID NO 2)

10. A pharmaceutical composition comprising the antibody of one of claims 1 or 9, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

11. A protective monoclonal antibody to lipoteichoic acid of Gram positive bacteria, wherein the antibody enhances survival in a lethal animal model by 10% or more.

12. The protective monoclonal antibody of claim 11, wherein the antibody binds to a peptide sequence selected from the group consisting of:

15 W R M Y F S H R H A H L R S P and (SEQ ID NO:1) W H W R H R I P L Q L A A G R. (SEQ ID NO:2)

13. A pharmaceutical composition comprising the antibody of claim 11, or fragments, regions, or derivatives thereof, and a pharmaceutically acceptable carrier.

14. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 10 or 13.

15. A method for preventing infections caused by Gram positive infections in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 10 or 13.

16. An lipoteichoic acid epitope peptide mimic comprising a peptide sequence selected from the group consisting of:

16 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

17. A peptide encoded by the DNA of the variable region of the anti-lipoteichoic antibody of FIG. 12 or a sequence that is at least 70% homologous to that DNA.

18. The peptide of claim 17 wherein the variable region on a chain is selected from the group consisting of the heavy chain and light chain.

19. The peptide of claim 17 wherein the DNA of the variable region encodes one or more of the Complementarity Determining Regions.

20. The peptide of claim 19 wherein the variable region is on a chain selected from

the group consisting of the heavy chain and light chain.

21. A peptide characterized by amino acids corresponding to one or more of the Complementarity Determining Regions of the variable region of the anti-lipoteichoic antibody of FIG. 12 or amino acids that are at least 70% homologous to the Complementarity Determining Regions.

22. The peptide of claim 21 wherein the variable region is selected from the group consisting of the heavy chain and the light chain.

23. A pharmaceutical composition comprising the peptides of any of claims 16-22 and a pharmaceutically acceptable carrier.

24. A method for treating a patient having an infection caused by a Gram positive bacteria comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 23.

25. A method for preventing infections caused by Gram positive bacteria in a patient comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of claim 23.

26. A vaccine for preventing infections caused by Gram positive bacteria comprising a lipoteichoic acid antigen and a pharmaceutically acceptable carrier.

27. The vaccine of claim 26 wherein the lipoteichoic acid antigen comprises the epitope of the antigen or an epitope mimic.

28. The vaccine of claim 26 wherein the epitope is a peptide sequence selected from the group consisting of:

17 (a) W R M Y F S H R H A H L R S P (SEQ ID NO 1) (b) W H W R H R I P L Q L A A G R, and (SEQ ID NO 2) (c) peptide sequences that are sub- stantially homologous to the sequences of (a) or (b).

29. An animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by Gram positive bacteria comprising the steps of: a) administering a lipid emulsion to at least two groups of suckling rodents; b) injecting into one group the composition to be tested and injecting into the other group a control substance; c) administering through a catheter an amount of Gram positive bacteria sufficient to cause lethal sepsis; d) leaving the catheter under the skin of the rodent; and d) assessing the affect of administration of the composition on either or both bacteremia and survival, wherein compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by Gram positive bacteria.

30. The method of claim 29 wherein the composition to be tested is an antibody to lipoteichoic acid of Gram positive bacteria or fragments thereof.

31. The method of claim 29 wherein the Gram positive bacteria is selected from the group consisting of Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus hominus, Staphylococcus aureus, Staphylococcus mutans, Staphylococcus faecalis, and Staphylococcus pyogenes.

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Welcher, Andrew A., et al. 435/69.1; 435/325 435/6 435/7.1 514/12 514/44 530/350 536/23.5 C12P021/02 C12N005/06 C12Q001/68 G01N033/53 C07H021/04 A61K048/00 C07K014/705.

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Terms	Documents
L5 and L4	48

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L17: Entry 19 of 54 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180111 B1
TITLE: Vaccine delivery system

Detailed Description Text (109):
Western blotting. Blebosome lysates (approximately ug of total protein) were analyzed by SDS-PAGE and Western blot with the OspA-specific mAb H5332 (Green, B. A., T. Quinn-Dey, and G. W. Zlotnick. 1987. Biologic activities of antibody to a peptidoglycan-asociated lipoprotein of Haemophilus influenzae against multiple clinical isolates of H. influenzae type b. Infect. Immun. 55:2878.). Expression of OspA was compared to purified OspA lipoprotein, kindly provided by Dr. L. Erdile (Connaught Laboratories, Inc., Swiftwater, Pa.). Protein bands reacting with H5332 were visualized after incubation with a secondary antibody (goat anti-mouse IgG conjugated to horseradish peroxidase) using the nehanced chemiluminescent detection (ECL) system (Amersham Corp., Arlington Heights, Ill.) according to the manufacturer's instructions.

L16: Entry 4 of 9 File: USPT Apr 25, 2000

DOCUMENT-IDENTIFIER: US 6054431 A
TITLE: Anti-gram-positive bacterial methods and materials

Detailed Description Text (23):
Without being bound by a theory of the invention, it is believed that BPI protein product may have several mechanisms of action. BPI protein product may act directly on the cell walls of gram-positive bacteria by binding to LPS-like molecules such as cell wall peptidoglycans and teichoic acid. If BPI is allowed to reach the inner cytoplasmic membrane, the amphipathic nature of BPI may allow it to penetrate the cytoplasmic membrane and exert a bactericidal effect. Thus, agents that act on or disrupt the cell walls of bacteria such as antibiotics, detergents or surfactants, anti-peptidoglycan antibodies, anti-lipoteichoic acid antibodies and lysozyme, may potentiate the activity of BPI by allowing access to the inner cytoplasmic membrane.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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With an indication in relation to deposited biological material furnished under Rule 13bis separately from the description.

(54) Title: OPSONIC AND PROTECTIVE MONOCLONAL AND CHIMERIC ANTIBODIES SPECIFIC FOR LIPOTEICHOIC ACID OF GRAM POSITIVE BACTERIA

96-110 ANTI-STAPH (HAY) HEAVY CHAIN VARIABLE REGION (TYPE IIIA)

GAAGTGATGCTGGTGGAGTCTGGGTGGAGGATTGGTGCAGCCTAAAGGGTCATTGAAACTCTCATGTGCAGCCTCTGGATTCACCTTCAAT SEQ ID NO.86
E V M L V E S G G G L V Q P K G S L K L S C A A S G F T F N SEQ ID NO.87

AACTACGCCATGAAT TGGGTCCGCCAGGCTCCAGGGAAAGGGTTTGGAATGGGTTGCT SEQ ID NO.88
N Y A M N W V R Q A P G K G L E W V A SEQ ID NO.89

CGCATAAGAAGTAAAAGTAATAATTATGCAACATTTTATGCCGATTCAGTGAAAGAC SEQ ID NO.90
R I R S K S N N Y A T F Y A D S V K D SEQ ID NO.91

ACGTTCACCATCTCCAGAGATGATTCACAAAGCATGCTCTATCTGCAAATGAACAACTTGAAAACTGAGGACACAGCCATGTATTACTGTGTGAGA SEQ ID NO.92
R F T I S R D D S Q S M L Y L Q M N N L K T E D T A M Y Y C V R SEQ ID NO.93

CGGGGGGCTTCAGGGACTGACTATGCTATGGACTAC TCGGGTCAAGGAACCTCACTCACCGTCTCCTCA SEQ ID NO.94
R G A S G I D Y A M D Y W G Q G T S L T V S S SEQ ID NO.95

96-110 ANTI-STAPH (HAY) LIGHT CHAIN VARIABLE REGION (TYPE VI)

CAAATTGTTCTCTCCCAGTCTCCAGCAATCCTGTCTGCATCTCCAGGGGAAAAGGTCACAATGACTTGC SEQ ID NO.96
Q I V L S Q S P A I L S A S P G E K V T M T C SEQ ID NO.97

AGGGCCAGCTCAAGTGTAAATTACATGCAC SEQ ID NO.98
R A S S S V N Y M H SEQ ID NO.99

TGGTACCAGCAGAAGCCAGGATCCTCCCCCAAACCCTGGATTTCT GCCACATCCAACCTGGCTTCT SEQ ID NO.100
W Y Q Q K P G S S P K P W I S A T S N L A S SEQ ID NO.101

GGAGTCCCTGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGCAGAGTGGAGGCTGAAGATGCTGCCACTTATTACTGC SEQ ID NO.102
G V P A R F S G S G S G T S Y S L T I S R V E A E D A A T Y Y C SEQ ID NO.103

CAGCAGTGGAGTAGTAACCCACCCACG TTCGGAGGGGGGACCATGCTGGAAATAAGA SEQ ID NO.104
Q Q W S S N P F T F G G G T M L E I R SEQ ID NO.105

CDR Regions Underlined

(57) Abstract

The present invention encompasses monoclonal and chimeric antibodies that bind to lipoteichoic acid of Gram positive bacteria. The antibodies also bind to whole bacteria and enhance phagocytosis and killing of the bacteria *in vitro* and enhance protection from lethal infection *in vivo*. The mouse monoclonal antibody has been humanized and the resulting chimeric antibody provides a previously unknown means to diagnose, prevent and/or treat infections caused by gram positive bacteria bearing lipoteichoic acid. This invention also encompasses a peptide mimic of the lipoteichoic acid epitope binding site defined by the monoclonal antibody. This epitope or epitope peptide mimic identifies other antibodies that may bind to the lipoteichoic acid epitope. Moreover, the epitope or epitope peptide mimic provides a valuable substrate for the generation of vaccines or other therapeutics.

First Hit

L6: Entry 47 of 48 File: DWPI Feb 20, 2003

DERWENT-ACC-NO: 1999-095329
DERWENT-WEEK: 200427

TITLE: New antibodies to lipoteichoic acid of gram positive bacteria - used to develop products for the diagnosis, prevention and treatment of infections caused by gram positive bacteria

INVENTOR: FISCHER, G W; SCHUMAN, R F ; STINSON, J L ; WONG, H ; STINSON, J R

PATENT-ASSIGNEE: JACKSON FOUND ADVANCEMENT MILITARY MED (JACKN), SUNOL MOLECULAR CORP (SUNON), JACKSON FOUND HENRY M (JACKN)

PRIORITY-DATA: 1997US-049871P (June 16, 1997), 1998US-0097055 (June 15, 1998), 2001US-0893615 (June 29, 2001), 2003US-0601171 (June 23, 2003), 2002AU-0300698 (August 21, 2002)

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PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	AU 2002300698 A1	February 20, 2003		000	C07K016/00
☐	WO 9857994 A2	December 23, 1998	E	149	C07K016/00
☐	AU 9881440 A	January 4, 1999		000	C07K016/00
☐	EP 986577 A2	March 22, 2000	E	000	C07K016/00
☐	JP 2002503966 W	February 5, 2002		124	C12N015/02
☐	US 20020082395 A1	June 27, 2002		000	C12P021/08
☐	US 6610293 B1	August 26, 2003		000	C12P021/08
☐	US 20040013673 A1	January 22, 2004		000	A61K039/40

DESIGNATED-STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU2002300698A1	June 16, 1998	1998AU-0081440	Div ex
AU2002300698A1	August 21, 2002	2002AU-0300698	
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AU 9881440A	June 16, 1998	1998AU-0081440	
AU 9881440A		WO 9857994	Based on

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EP 986577A2		WO 9857994	Based on
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JP2002503966W		WO 9857994	Based on
US20020082395A1	June 16, 1997	1997US-049871P	Provisional
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US20020082395A1	June 29, 2001	2001US-0893615	
US 6610293B1	June 16, 1997	1997US-049871P	Provisional
US 6610293B1	June 15, 1998	1998US-0097055	
US20040013673A1	June 16, 1997	1997US-049871P	Provisional
US20040013673A1	June 15, 1998	1998US-0097055	Cont of
US20040013673A1	June 23, 2003	2003US-0601171	
US20040013673A1		US 6610293	Cont of

INT-CL (IPC): A61 K 39/395; A61 K 39/40; A61 P 31/04; C07 K 7/00; C07 K 16/00; C07 K 16/12; C07 K 16/46; C08 B 37/00; C12 N 15/02; C12 P 21/08; C12 Q 1/18; G01 N 33/53

ABSTRACTED-PUB-NO: US20020082395A
BASIC-ABSTRACT:

A monoclonal antibody (MAb) to lipoteichoic acid (LA) of Gram positive (GP) bacteria, where the MAb: (a) binds to LA at a level that is twice background or greater, and (b) enhances the opsonisation of GP bacteria by 75% or more. Also claimed are: (1) a chimeric immunoglobulin comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to TA of GP bacteria; (2) an antibody to LA of GP GP bacteria where the antibody: (a) binds to LA at a level that is twice background or greater; (b) enhances the opsonisation of GP bacteria by 75% or more; and (c) binds to a peptide sequence selected from sequences (I) and (II): WRMYFSHRHAHLRSP (I) WHWRHRIPLQLAAGR (II) (3) a protective MAb to LA of GP bacteria, where the antibody enhances survival in a lethal animal model by 10% or more; (4) a LA epitope peptide mimic comprising a peptide sequence selected from (I), (II) and peptide sequences homologous to them; (5) a peptide encoded by a DNA of the variable region of the anti-LA antibody shown or a sequence that is at least 70% homologous to that DNA; (6) a peptide characterised by amino acids corresponding to one or more of the Complementarity Determining Regions (CDRs) of the variable region of the anti-LA antibody shown or amino acids that are at least 70% homologous homologous to the CDRs; (7) a vaccine for preventing infections caused by GP bacteria comprising a LA antigen and a carrier, and (8) an animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by GP bacteria comprising: (a) administering a lipid emulsion to at least 2 groups of suckling rodents; (b) injecting into one group the composition to be tested and injecting into the other group a control substance; (c) administering GP bacteria through a catheter to cause lethal sepsis; (d) leaving the catheter under the skin of the rodent; and (d) assessing the affect of administration of the composition on either or both bacteremia and survival; where compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by GP bacteria.

USE - The antibodies bind to whole bacteria and enhance phagocytosis and killing of the bacteria and enhance protection from lethal infection. The antibodies or peptides can be used for treating or preventing infections caused by GP bacteria

(claimed). They can also be used for the diagnosis of GP infections.

ABSTRACTED-PUB-NO: WO 9857994A
EQUIVALENT-ABSTRACTS:

A monoclonal antibody (MAb) to lipoteichoic acid (LA) of Gram positive (GP) bacteria, where the MAb: (a) binds to LA at a level that is twice background or greater, and (b) enhances the opsonisation of GP bacteria by 75% or more. Also claimed are: (1) a chimeric immunoglobulin comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region having specificity to TA of GP bacteria; (2) an antibody to LA of GP GP bacteria where the antibody: (a) binds to LA at a level that is twice background or greater; (b) enhances the opsonisation of GP bacteria by 75% or more; and (c) binds to a peptide sequence selected from sequences (I) and (II): WRMYFSHRHAHLRSP (I) WHWRHRIPLQLAAGR (II) (3) a protective MAb to LA of GP bacteria, where the antibody enhances survival in a lethal animal model by 10% or more; (4) a LA epitope peptide mimic comprising a peptide sequence selected from (I), (II) and peptide sequences homologous to them; (5) a peptide encoded by a DNA of the variable region of the anti-LA antibody shown or a sequence that is at least 70% homologous to that DNA; (6) a peptide characterised by amino acids corresponding to one or more of the Complementarity Determining Regions (CDRs) of the variable region of the anti-LA antibody shown or amino acids that are at least 70% homologous homologous to the CDRs; (7) a vaccine for preventing infections caused by GP bacteria comprising a LA antigen and a carrier, and (8) an animal lethality test for determining the in vivo activity of a composition to treat or prevent infections by GP bacteria comprising: (a) administering a lipid emulsion to at least 2 groups of suckling rodents; (b) injecting into one group the composition to be tested and injecting into the other group a control substance; (c) administering GP bacteria through a catheter to cause lethal sepsis; (d) leaving the catheter under the skin of the rodent; and (d) assessing the affect of administration of the composition on either or both bacteremia and survival; where compositions that either reduce bacteremia or enhance survival are useful to treat or prevent infections by GP bacteria.

USE - The antibodies bind to whole bacteria and enhance phagocytosis and killing of the bacteria and enhance protection from lethal infection. The antibodies or peptides can be used for treating or preventing infections caused by GP bacteria (claimed). They can also be used for the diagnosis of GP infections.

CHOSEN-DRAWING: Dwg.0/22

DERWENT-CLASS: B04 D16
CPI-CODES: B04-C01; B04-F10; B04-G01; B12-K04A4; B14-A01B; B14-S11B; D05-H04; D05-H07; D05-H11A;

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☐ 3. 20040028688. 05 Jul 02. 12 Feb 04. Vaccine for the prevention of bacterial infection of the bovine mammary gland. Guidry, Albert, et al. 424/184.1; A61K039/00 A61K039/38 A61K039/085.

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Terms	Documents
L11 and L8 and L9 and L10	56

First Hit Fwd Refs

L12: Entry 45 of 56 File: USPT Nov 27, 2001

US-PAT-NO: 6322788
DOCUMENT-IDENTIFIER: US 6322788 B1

TITLE: Anti-bacterial antibodies and methods of use

DATE-ISSUED: November 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kim; Stanley Arthur	Wellington	FL	33414	

APPL-NO: 09/ 378147 [PALM]
DATE FILED: August 20, 1999

PARENT-CASE:
REFERENCE TO RELATED APPLICATIONS The present application claims the benefit of U.S. Provisional Application Ser. No. 60/097,291 filed Aug. 20, 1998, which is incorporated herein by reference.

INT-CL: [07] A61 K 39/40

US-CL-ISSUED: 424/164.1; 424/133.1, 424/150.1, 424/165.1, 424/178.1, 530/387.1, 530/388.1, 530/388.4, 530/389.5
US-CL-CURRENT: 424/164.1; 424/133.1, 424/150.1, 424/165.1, 424/178.1, 530/387.1, 530/388.1, 530/388.4, 530/389.5

FIELD-OF-SEARCH: 530/387.1, 530/388.1, 530/388.4, 530/389.5, 424/141.1, 424/150.1, 424/164.1, 424/165.1, 424/178.1, 424/133.1

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5770208	July 1998	Fattom et al.	

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ART-UNIT: 168

PRIMARY-EXAMINER: Scheiner; Laurie

ATTY-AGENT-FIRM: Kim; Stanley A.

ABSTRACT:

Compositions containing a purified antibody having both an antigen-binding portion specific for a bacterial antigen and a constant region that does not bind bacterial Fc-binding proteins are disclosed. Also disclosed are compositions and methods for treating and preventing bacterial infections in animals and humans.

13 Claims, 0 Drawing figures

First Hit

L6: Entry 1 of 48 File: PGPB Mar 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040052779
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040052779 A1

TITLE: Opsonic monoclonal and chimeric antibodies specific for lipoteichoic acid of Gram positive bacteria

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

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Schuman, Richard F.	Gaithersburg	MD	US	
Mond, James J.	Silver Spring	MD	US	
Lees, Andrew	Silver Spring	MD	US	
Fischer, Gerald Walter	Bethesda	MD	US	

APPL-NO: 10/ 323926 [PALM]
DATE FILED: December 20, 2002

RELATED-US-APPL-DATA:
Application is a non-provisional-of-provisional application 60/343503, filed December 21, 2001,

INT-CL: [07] A61 K 39/395, C07 K 16/44

US-CL-PUBLISHED: 424/130.1; 530/388.1
US-CL-CURRENT: 424/130.1; 530/388.1

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

The present invention encompasses monoclonal antibodies that bind to lipoteichoic acid (LTA) of Gram positive bacteria. The antibodies also bind to whole bacteria and and enhance phagocytosis and killing of the bacteria in vitro. The invention also provides antibodies having human sequences (chimeric, humanized and human antibodies). The invention also sets forth the variable regions of three antibodies within the invention and presents the striking homology between them.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is based on and claims the benefit of U.S. Provisional Application S. No. 60/343,503, filed Dec. 21, 2001 (Attorney Docket No. 7787.6008). The entire disclosure of this provisional application is relied upon and incorporated by reference herein. This application also relates to U.S. Pat. No. 5,571,511, U.S. Pat. No. 5,955,074, and U.S. patent application Serial No.

09/097,055, filed Jun. 15, 1998, all of which are specifically incorporated herein by reference.

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☐ 41. 20020037557. 13 Mar 01. 28 Mar 02. Fibroblast growth factor-like molecules and uses thereof. Jing, Shuqian, et al. 435/69.4; 435/325 435/335 435/7.1 530/388.24 530/399 536/23.5 800/14 G01N033/53 A01K067/027 C07H021/04 C12N005/06.

☐ 42. 20020037524. 21 Jun 01. 28 Mar 02. IL-17 like molecules and uses thereof. Medlock, Eugene, et al. 435/6; 435/320.1 435/325 435/69.1 530/350 536/23.5 C12Q001/68 C07H021/04 C12N005/06 C12P021/02.

☐ 43. 20020015981. 27 Mar 01. 07 Feb 02. Beta-like glycoprotein hormone polypeptide and heterodimer. Paszty, Christopher J.R., et al. 435/69.4; 435/325 435/6 435/7.92 514/12 514/44 530/397 536/23.5 800/8 C12Q001/68 G01N033/53 A01K067/00 C07H021/04 C12P021/02 C12N005/06 A61K048/00 A61K038/22 C07K014/575.

☐ 44. 20020009776. 22 Mar 01. 24 Jan 02. Fibroblast growth factor receptor-like molecules and uses thereof. Saris, Christiaan M., et al. 435/69.1; 435/325 435/334 435/7.1 530/350 530/388.22 536/23.5 C12P021/02 C07K014/705 G01N033/53 C12N005/06 C07H021/04.

☐ 45. 20010035406. 31 May 01. 01 Nov 01. Apparatus for RF active compositions used in adhesion, bonding, and coating. Ryan, William J., et al. 219/634; 219/660 H05B006/06.

☐ 46. 6610293. 15 Jun 98; 26 Aug 03. Opsonic and protective monoclonal and chimeric antibodies specific for lipoteichoic acid of gram positive bacteria. Fischer; Gerald W., et al. 424/133.1; 424/150.1 530/387.3 530/388.4. C12P021/08 A61K039/40 A61K039/395.

☐ 47. US20020082395A. New antibodies to lipoteichoic acid of gram positive bacteria - used to develop products for the diagnosis, prevention and treatment of infections caused by gram positive bacteria. FISCHER, G W, et al. A61K039/395 A61K039/40 A61P031/04 C07K007/00 C07K016/00 C07K016/12 C07K016/46 C08B037/00 C12N015/02 C12P021/08 C12Q001/18 G01N033/53.

☐ 48. BE 837223A. Moulding panels of constant thickness with variable stiffness - by local adjustment of foam crosslink density. B29C003/00 B29C067/20 B29C067/22 B29D003/02 B29D027/00 B29J000/00 B29K075/00 B29L031/58 B32B005/18 B32B031/12 C08G018/14 C08J005/24 C08J009/40.

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Terms	Documents
L5 and L4	48

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Search Results - Record(s) 1 through 12 of 12 returned.

☐ 1. Document ID: US 6221365 B1

Using default format because multiple data bases are involved.

L8: Entry 1 of 12 File: USPT Apr 24, 2001

US-PAT-NO: 6221365
DOCUMENT-IDENTIFIER: US 6221365 B1

TITLE: NucA protein of Haemophilus influenzae

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jones; Kevin F.	New York	NY		

US-CL-CURRENT: 424/256.1; 424/184.1, 424/185.1, 424/190.1, 435/196, 435/320.1, 435/69.1, 435/69.3, 435/71.1, 530/350, 536/23.1, 536/23.7, 536/24.3, 536/24.32

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 2. Document ID: US 5955596 A

L8: Entry 2 of 12 File: USPT Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5955596 A
TITLE: NucA protein of Haemophilus influenzae and the gene encoding that protein

Detailed Description Text (168):
Groups P174 and P175 received anti-sera from rabbits immunized with a 16 kD NTHi protein designated P6 (also known as HiPAL or PBOMP-1 (22)). Group P176 received a monoclonal antibody raised against NTHi polyribosyl ribitol phosphate (PRP). Group P177 received PCM buffer (10 mM NaPO.sub.4, pH 7.4, 150 mM NaCl, 0.5 mM MgCl.sub.2, 0.15 mM CaCl.sub.2) as a buffer control. All dilutions of sera and cells were done in PCM buffer. About 23 hours later, they were challenged IP with 49.5 organisms (0.1 ml) of virulent H. influenzae type b, Eagan strain. Then, 20-24 hours post-challenge, the infant rats were bled and plated for bacterial counts. Tails were nicked and 10 .mu.l blood taken up with a P20 Rainin Pipetman and diluted into 90 .mu.l PCM buffer at RT. Dilutions were vortexed and held at 4.degree. C. until further dilutions were made and 10 .mu.l of each dilution was plated onto chocolate agar in duplicate. Plates were incubated in 5% CO.sub.2 incubator at 36.5.degree.

C. overnight. The results of the protection study are set forth in Table 8:

☐ 3. Document ID: US 5192540 A

L8: Entry 3 of 12 File: USPT Mar 9, 1993

DOCUMENT-IDENTIFIER: US 5192540 A
TITLE: Haemophilus influenzae type b oxidized polysaccharide-outer membrane protein conjugate vaccine

CLAIMS:

6. A method of eliciting antibody response to the polyribosyl-ribitol-phosphate polysaccharide and the 38,000 daltons and 40,000 daltons outer membrane protein of Haemophilus influenzae type b in warm-blooded animals, which comprises administering to said animals an immunogenic amount of the vaccine of claim 4.

☐ 4. Document ID: US 4954449 A

L8: Entry 4 of 12 File: USPT Sep 4, 1990

DOCUMENT-IDENTIFIER: US 4954449 A
TITLE: Human monoclonal antibody reactive with polyribosylribitol phosphate

Brief Summary Text (2):
This invention relates to a novel self-reproducing carrier cell and more specifically to a carrier cell containing genes for the production of human monoclonal antibody reactive with antigenic polyribosylribitol phosphate capsular polysaccharide, to the antibody, to a process of preparing the antibody from the carrier cell, to diagnostic, prophylactic and therapeutic methods and compositions employing this antibody, and to a research composition employing this antibody.

Detailed Description Text (7):
The splenic lymphocytes were thawed, hybridomas were prepared and purified anti-PRP was obtained using routine procedures. The splenic lymphocytes were fused with HFB-1 in the presence of a suitable fusion promoter, which in this case was 50% polyethylene glycol (MW, 1400), generally according to the now standard technique of Olsson and Kaplan described in Proc. Nat'l. Acad. Sci., USA, 77:5429 (1980), which is hereby incorporated by reference into this description. The early hybrids were grown in accordance with a customary procedure in microcultures in hypoxanthine-aminopterin-thymidine medium, which kills all HGPRT- parental myelomas. After 14 days of culture, the supernatants of the microcultures were screened by enzyme immunoassay for the presence of antibodies that bind to PRP

capsular polysaccharide of the bacterium Haemophilus influenzae type b. A positive culture was cloned by limiting dilution on a feeder cell, which in this case was irradiated mouse tumor macrophages (P388D1). After 19 days, the microcultures were retested by enzyme immunoassay to identify clones that secreted monoclonal anti-PRP antibody. One clone designated C3,H12 by us was selected and grown in large-scale culture. By Ouchterlony analysis, the antibodies of this clone were determined to be be of the IgG isotype, and by using Protein A Sepharose affinity chromatography, purified IgG anti-PRP antibody was obtained. The subclass of this antibody appears to be IgG1. As indicated earlier, now that we have described the procedures for obtaining this carrier cell, we believe that a person skilled in this art will be able to reproduce our work and obtain a self-reproducing carrier cell containing genes that produce human monoclonal antibody reactive with antigenic polyribosylribitol phosphate capsular polysaccharide.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 5. Document ID: US 4761283 A

L8: Entry 5 of 12 File: USPT Aug 2, 1988

DOCUMENT-IDENTIFIER: US 4761283 A
TITLE: Immunogenic conjugates

CLAIMS:

32. A vaccine that elicits effective levels of anti-polyribosyl ribitol phosphate antibody formations in young warm-blooded mammals comprising an immunogenic amount of the conjugate of claim 1 and a pharmaceutically acceptable carrier.

33. A vaccine that elicits effective levels of anti-polyribosyl ribitol phosphate antibody formations in young warm-blooded mammals comprising an immunogenic amount of the conjugate of claim 4 and a pharmaceutically acceptable carrier.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 6. Document ID: US 4744982 A

L8: Entry 6 of 12 File: USPT May 17, 1988

DOCUMENT-IDENTIFIER: US 4744982 A
TITLE: Human monoclonal antibody reactive with polyribosylribitol phosphate

Brief Summary Text (2):
This invention relates to a novel self-reproducing carrier cell and more specifically to a carrier cell containing genes for the production of human monoclonal antibody reactive with antigenic polyribosylribitol phosphate capsular polysaccharide, to the antibody, to a process of preparing the antibody from the

carrier cell, to diagnostic, prophylactic and therapeutic methods and compositions employing this antibody, and to a research composition employing this antibody.

Brief Summary Text (30):
The splenic lymphocytes were thawed, hybridomas were prepared and purified anti-PRP was obtained using routine procedures. The splenic lymphocytes were fused with HFB-1 in the presence of a suitable fusion promoter, which in this case was 50% polyethylene glycol (MW, 1400), generally according to the now standard technique of Olsson and Kaplan described in Proc. Nat'l. Acad. Sci., USA, 77:5429 (1980), which is hereby incorporated by reference into this description. The early hybrids were grown in accordance with a customary procedure in microcultures in hypoxanthine-aminopterin-thymidine medium, which kills all HGPRT- parental myelomas. After 14 days of culture, the supernatants of the microcultures were screened by enzyme immunoassay for the presence of antibodies that bind to PRP capsular polysaccharide of the bacterium Haemophilus influenzae type b. A positive culture was cloned by limiting dilution on a feeder cell, which in this case was irradiated mouse tumor macrophages (P388D1). After 19 days, the microcultures were retested by enzyme immunoassay to identify clones that secreted monoclonal anti-PRP antibody. One clone designated C3,H12 by us was selected and grown in large-scale culture. By Ouchterlony analysis, the antibodies of this clone were determined to be of the IgG isotype, and by using Protein A Sepharose affinity chromatography, purified IgG anti-PRP antibody was obtained. The subclass of this antibody appears to be IgG1. As indicated earlier, now that we have described the procedures for obtaining this carrier cell, we believe that a person skilled in this art will be able to reproduce our work and obtain a self-reproducing carrier cell containing genes that produce human monoclonal antibody reactive with antigenic polyribosylribitol phosphate capsular polysaccharide.

CLAIMS:

1. A human monoclonal antibody reactive with antigenic polyribosylribitol phosphate capsular polysaccharide, said antibody produced by a self-reproducing carrier cell containing genes that produce a human monoclonal antibody reactive with polyribosylribitol phosphate capsular polysaccharide.

☐ 7. Document ID: US 4474758 A

L8: Entry 7 of 12 File: USPT Oct 2, 1984

DOCUMENT-IDENTIFIER: US 4474758 A
TITLE: Haemophilus influenzae type b and pertussis outer membrane component combined vaccine

Abstract Text (1):
A combined vaccine for eliciting polyribosyl ribitol phosphate (PRP) antibody formations in warm-blooded animals has been invented. The combined vaccine comprises the capsular polysaccharide PRP isolated and purified from Haemophilus influenzae type b and antigens isolated and purified from an outer membrane component of Bordetella pertussis.

Brief Summary Text (3):

This invention relates to a combined vaccine for eliciting polyribosyl ribitol phosphate (PRP) antibody formations in warm-blooded animals. This invention also relates to a method for inducing active immunization in warm-blooded animals against systemic infection caused by the pathogen H. influenzae type b.

CLAIMS:

1. A combined vaccine for eliciting polyribosyl ribitol phosphate (PRP) antibody formations in warm-blooded animals comprising the capsular polysaccharide PRP isolated and purified from Haemophilus influenzae type b and antigens isolated and purified from an outer membrane component of Bordetella pertussis.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 8. Document ID: US 4196192 A

L8: Entry 8 of 12 File: USPT Apr 1, 1980

DOCUMENT-IDENTIFIER: US 4196192 A
TITLE: Combined Haemophilus influenzae type b and pertussis vaccine

CLAIMS:

1. A combined vaccine that elicits effective levels of anti-PRP (polyribosyl ribitol phosphate) and anti-pertussis antibody formations in young warm-blooded animals which consists of polyribosyl ribitol phosphate isolated and purified from the capsular polysaccharide of Haemophilus influenzae type b by adding hydroxylapatite in about 20 millimolar phosphate buffer at pH from about 6.7 to about 6.9, mixing at a temperature of about 1.degree. to 4.degree. C., centrifuging, and removing the supernatant and repeating the foregoing procedure at least 2 more times, filtering the supernatant, dializing against pyrogen free distilled water, and then lyophilizing; and Bordetella pertussis antigens.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 9. Document ID: EP 101562 A2

L8: Entry 9 of 12 File: EPAB Feb 29, 1984

PUB-NO: EP000101562A2
DOCUMENT-IDENTIFIER: EP 101562 A2
TITLE: Combined haemophilus influenzae and diphtheria, pertussis, tetanus vaccine.

PUBN-DATE: February 29, 1984

INVENTOR-INFORMATION:
NAME COUNTRY

KUO, JOSEPH S C

US-CL-CURRENT: 424/203.1
INT-CL (IPC): A61K 39/02; A61K 39/05; A61K 39/08; A61K 39/10; A61K 39/102
EUR-CL (EPC): A61K039/116

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 10. Document ID: JP 59089697 A, US 4744982 A, US 4954449 A

L8: Entry 10 of 12 File: DWPI May 23, 1984

DERWENT-ACC-NO: 1984-221330
DERWENT-WEEK: 198436
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Human mono-clonal antibody - reactive with poly-ribosyl lipidol phosphate capsule polysaccharide antigen

PRIORITY-DATA: 1982US-0411115 (August 24, 1982), 1988US-0155437 (February 12, 1988)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 59089697 A	May 23, 1984		008	
US 4744982 A	May 17, 1988		000	
US 4954449 A	September 4, 1990		000	

INT-CL (IPC): A61K 39/39; C07G 7/00; C07K 15/00; C12N 5/00; C12N 15/00; C12P 21/00; C12Q 1/02; G01N 33/53

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 11. Document ID: EP 101562 A, AU 8318157 A, CA 1209036 A, ES 8502339 A, JP 59053431 A

L8: Entry 11 of 12 File: DWPI Feb 29, 1984

DERWENT-ACC-NO: 1984-057599
DERWENT-WEEK: 198410
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Vaccine for active immunisation against Haemophilus influenzae type B - contains H influenzae capsular polysaccharide combined with diphtheria, pertussis and tetanus vaccine

INVENTOR: KUO, J S C

PRIORITY-DATA: 1982US-0409776 (August 20, 1982)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 101562 A	February 29, 1984	E	010	
AU 8318157 A	February 23, 1984		000	

CA 1209036 A	August 5, 1986	000
ES 8502339 A	April 1, 1985	000
JP 59053431 A	March 28, 1984	000

INT-CL (IPC): A61K 39/02

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 12. Document ID: EP 80021 A, AU 8290714 A, CA 1192840 A, DE 3269381 G, DK 8205148 A, EP 80021 B, ES 8401722 A, JP 58092618 A, US 4474758 A, ZA 8208517 A

L8: Entry 12 of 12 File: DWPI Jun 1, 1983

DERWENT-ACC-NO: 1983-54296K
DERWENT-WEEK: 198323
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Vaccine against meningitis in children - contg. poly:saccharide from haemophilus influenzae type B and pertussis membrane component

INVENTOR: KUO, J S C; MONJI, N R F

PRIORITY-DATA: 1981US-0323523 (November 19, 1981)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 80021 A	June 1, 1983	E	013	
AU 8290714 A	May 26, 1983		000	
CA 1192840 A	September 3, 1985		000	
DE 3269381 G	April 3, 1986		000	
DK 8205148 A	July 18, 1983		000	
EP 80021 B	February 26, 1986	E	000	
ES 8401722 A	March 16, 1984		000	
JP 58092618 A	June 2, 1983		000	
US 4474758 A	October 2, 1984		000	
ZA 8208517 A	August 5, 1983		000	

INT-CL (IPC): A61K 39/11; C08B 0/00; C12N 0/00; C12P 0/00; C12R 0/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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Terms	Documents
polyribosyl$ near5 antibod$	12

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DIALOG(R)File 73:EMBASE

06705624 EMBASE No: 1996370573
Monoclonal **antibody-based therapy**
Von Mehren M.; Weiner L.M.
Fox Chase Cancer Center, 7701 Burholme Avenue,Philadelphia, PA 19111
United States
Current Opinion in Oncology (CURR. OPIN. ONCOL.) (United States) 1996
, 8/6 (493-498)
CODEN: CUOOE ISSN: 1040-8746
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Monoclonal antibodies have been developed for cancer therapy because they specifically target tumor-related antigens. The current design of antibodies and delivery strategies seeks to overcome the obstacles encountered in delivering antibodies to their targets. Protein engineering techniques to **humanize** murine antibodies diminishes the immune response, which develops against murine **monoclonal** antibodies, allowing for multiple doses. Antibodies linked to vasoactive substances or conjugated to liposomes increase antibody and drug localization to tumors. Altering the sizes of antibodies and the methods by which they are conjugated to radioactive isotopes have delineated methods to increase efficacy and decrease toxicity. Tumor growth factors increasingly are being targeted by antibody-based therapeutics. To enhance immune activation of cytotoxic effector cells, bispecific antibodies and antibodies linked to superantigens are being examined. Prodrugs are being converted to their active compounds at the tumor site by antibodies conjugated to enzymes. Finally, intrabodies which can bind to intracellular proteins and are important for the malignant phenotype of the cell, are being developed.

DRUG DESCRIPTORS:
* **monoclonal** antibody--adverse drug reaction--ae; * **monoclonal** antibody --drug therapy--dt; * **monoclonal** antibody--clinical trial--ct; *tumor antigen
Fc receptor; bispecific antibody; cancer growth factor; carboxypeptidase a; carcinoembryonic antigen **monoclonal** antibody; epidermal growth factor receptor; hybrid protein; immunoglobulin f(ab')2 fragment; immunoglobulin f(ab) fragment; immunoglobulin g antibody; immunoglobulin g1; immunotoxin; interleukin 6 antibody--drug therapy--dt; iodine 131; liposome; methotrexate; prodrug; pseudomonas exotoxin; **staphylococcus** enterotoxin a ; superantigen; vasoactive agent; yttrium 90
MEDICAL DESCRIPTORS:
*breast cancer--drug therapy--dt; *cancer immunotherapy; *immune response article; cancer chemotherapy; clinical trial; colorectal carcinoma --diagnosis--di; drug design; drug targeting; effector cell; genetic engineering; human; intraperitoneal drug administration; intravenous drug administration; isotope labeling; liver metastasis--diagnosis--di; liver metastasis--complication--di; multiple myeloma--drug therapy--dt; nonhuman; oncogene; priority journal; side effect; drug delivery system
CAS REGISTRY NO.: 11075-15-5 (carboxypeptidase a); 10043-66-0, 15124-39-7 (iodine 131); 15475-56-6, 59-05-2, 7413-34-5 (methotrexate); 37337-57-8 (**staphylococcus** enterotoxin a); 10098-91-6 (yttrium 90)
SECTION HEADINGS:
016 Cancer
023 Nuclear Medicine
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reaction Titles

8/9/21 (Item 1 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01779194 SUPPLIER NUMBER: 20902118 (THIS IS THE FULL TEXT)
Nitric oxide and septic shock: from bench to bedside.
Kuhl, Sarah J.; Rosen, Hen[illegible]

The Western Journal of Medicine, v168, n3, p176(6)
March,
1998
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0093-0415
LANGUAGE: English RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE:
Professional
WORD COUNT: 4335 LINE COUNT: 00379

AUTHOR ABSTRACT: Refractory hypotension with end-organ hypoperfusion is an ominous feature of inflammatory shock. In the past fifteen years, nitric oxide (a diffusible, short-lived product of arginine metabolism) has been found to be an important regulatory molecule in several areas of metabolism, Including vascular tone control. Vascular endothelial cells constitutively produce low levels of nitric oxide that regulate blood pressure by mediating adjacent smooth-muscle relaxation. In an inflammatory shock state, cytokines, like interleukin-1 and tumor necrosis factor-(Alpha), induce a separate, high-output form of the enzyme that synthesizes nitric oxide in both endothelial and smooth-muscle cells. The ensuing high rates of nitric oxide formation result in extensive smooth-muscle relaxation, pressor refractory vasodilation, and--ultimately--shock. The concept of the pathogenesis of inflammatory shock explains many limitations of current therapies and may foster the development of new interventions to mitigate the effects of nitric oxide overproduction in this syndrome. (Kuhl SJ, Rosen H. Nitric oxide and septic shock--from bench to bedside. West J Med 1998; 168:176-181)

TEXT:

Septic shock remains a clinical problem with high mortality rates, and therapy is mainly supportive. We review the evidence for the role of nitric oxide in mediating the hypotensive features of septic shock. Therapeutic implications are then discussed.

Case Presentation

A 72-year-old man with insulin-dependent diabetes mellitus was brought to the emergency department. He had been in his usual state of health on the evening before admission, but was confused and unable to get out of bed the following morning. On physical examination, the patient was stuporous and disoriented. His blood pressure was 95/50 mm of mercury; regular pulse, 110 beats per minute; and temperature, 38.3 (degrees) C (101 (degrees) F). Respiration was shallow at a rate of 22 per minute. His leukocyte count was 12 000, with a left shift; a urine gram stain identified many leukocytes and gram-negative rods per high power field. Despite broad spectrum antimicrobial therapy, vigorous volume resuscitation, and intravenous vasopressors, his condition continued to deteriorate: he experienced a further drop in blood pressure, the onset of adult respiratory distress syndrome, and oliguria. The patient died with cardiac arrhythmia. Blood cultures grew Escherichia coli, susceptible to all antibiotics that had been administered. Results of a postmortem examination showed multiple organ failure consistent with prolonged hypotension and sepsis. No additional predisposing factors to infection were discovered.

The Spectrum of Sepsis

The patient's initial presentation--which included fever, tachycardia, and hypotension--and his progression to pressor-refractory shock with multiple organ failure represents the continuum of the systemic inflammatory response to various agents. **Gram - positive** and noninfectious agents can produce a syndrome with characteristics indistinguishable from those of classic gram-negative sepsis; the syndrome has thus been named the systemic inflammatory response syndrome (SIRS).(1) Table 1(1) describes the progression of SIRS manifestations, from abnormal vital signs and an elevated or decreased leukocyte count or bandemia, through various degrees of end-stage organ dysfunction and pressor refractory hypotension. Our patient presented at a point late in this progression, and medical intervention was unsuccessful. A prominent feature of septic shock--severe refractory hypotension and its possible relationship with the recently recognized vasoregulatory molecule, nitric oxide (NO)--will be the focus of this review.

TABLE 1.--Definitions

Systemic inflammatory response syndrome (SIRS)

Premonitory SIRS

Abnormal vita[illegible]ns:
tachypnea, ta[illegible]rdia, hyper- or hypothermia
Early SIRS:
Above plus ev[illegible]e of early end organ dysfunction:
oliguria, hypo[illegible], confusion, elevated lactate.
SIRS with hypoten[illegible]:
Above plus hyp[illegible]sion responsive to fluid resuscitation
or pressor ag[illegible]
Refractory hypot[illegible]n:
SIRS with hyp[illegible]ion unresponsive to fluid resuscitation
or pressor ag
Sepsis and septi[illegible]ock are SIRS resulting from infection.

Normal Vasoregu[illegible]ry Properties of NO.

The discovery o[illegible], as a human regulatory molecule is relatively recent. In 1980, Furch[illegible]t and Zawadzki(2) found that the ability of acetylcholine to dila[illegible]rteries was dependent on a short-lived, low-molecular weight p[illegible]uct of endothelial cells, designated endothelium-derived r[illegible]xation factor (Figure 1). In 1987, endothelium-derived r[illegible]xation factor was reported to be NO.(3) Until that point, the inorganic [illegible]s of nitrogen were thought to have little or no role in normal human p[illegible]ology. We now recognize that endothelial cells continuously produce [illegible]vels of NO, to maintain normal vascular tone, and we have observed [illegible]ts that diminish endothelial production of NO, to cause hypertension and [illegible]soconstriction.(4) Furthermore, pharmacologic vasodilators, such as [illegible]lium nitroprusside and nitroglycerin, are believed to exert their effect[illegible]hrough the formation of NO.(5)

(Figure 1 ILLUS[illegible]TION OMITTED)

NO. Chemistry a[illegible] Cell Biology

NO, is unstable [illegible]d has a life span of a few seconds. Because of its short half-life, the [illegible]ects of NO must occur over short distances, and biologically active N[illegible]must be synthesized either within the cell (autocrine) or by c[illegible]nearby (paracrine). In aqueous solutions, such as plasma, NO, is oxid[illegible]ainly to nitrite,(6,7) which, in the presence of hemoglobin, is quick[illegible]idized to nitrate. Some of the physiologic characteristics of NO[illegible]e relate[illegible] to its ability to bind to heme. The binding of NO, to hem[illegible]n hemoglobin results in the accelerated degradation of NO, to nitrate, a[illegible]ture that may further limit the lifespan of NO, in the bloodstream. The [illegible]ding of NO to the heme of guanylate cyclase, a smooth-muscle enzyme, [illegible]celerates the conversion of guanosine triphosphate to cyclic guanosine m[illegible]phosphate. The resulting increased levels of cyclic guanosine monophosp[illegible]pparently mediate muscle cell relaxation in a manner that is not [illegible]characterized.(5)

Physiologic N[illegible] synthesized from arginine by an enzyme complex called NO. synthas[illegible]S (Figure 2). Three distinct NOS enzyme complexes have been describ[illegible]onal nitric oxide synthase (nNOS) is found in cells of the centra[illegible]vous syste[illegible] cells and is thought to support a neurotransmitter fu[illegible]n. A seco[illegible]--constitutive NOS (cNOS)--is in endothelial cells a[illegible] thought [illegible] play a role in the maintenance of normal vascular to[illegible]e third i[illegible] high output, inducible enzyme called inducible NOS (iNO[illegible]is comple[illegible] is found in many cell types but particularly endot[illegible] and vascular smooth-muscle cells. It is proposed that iNOS is the e[illegible] hat play[illegible] major role in septic hypotension.

(Figure 2 IL[illegible]TION OMITTED)

Increased NO [illegible]esis In [illegible]flammatory States

Several obse[illegible]s indicat[illegible] that nitrate production increases in humans in inflamma[illegible]ates. In [illegible] study of normal nitrate excretion in humans,(8) one stu[illegible]ject sere[illegible]spitously acquired infectious diarrhea and simultaneously [illegible]ited incr[illegible]ed nitrate excretion.(9) A second study(10) evaluate[illegible]te biosynthesis in renal cell carcinoma and melanoma patients [illegible]re receiv[illegible] high-dose interleukin-2 therapy, which frequently produce[illegible]brile, h[illegible]nsive state similar to septic shock. Nitrate excretion [illegible]ed dram[illegible]ally in these patients; the nitrate was derived from the s[illegible]rogens o[illegible]rginine that would be acted upon by the NOS enzyme comple[illegible]er study[illegible]) showed that in patients with septic shock, plasma nitr[illegible] nitrate [illegible]ncentrations are increased and correlate directly [illegible]ndotoxi[illegible]ncentration and cardiac output. The same concentratio[illegible]late inv[illegible]ely with systemic blood pressure, consistent with th[illegible] of NO. a[illegible]diator of the hemodynamic disturbances in s[illegible]

Inducible NO ase

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A Set of Mo Se ion

Gram-negati ga ive bacteria such as E. coli have an endotoxin or lipo ponent to their outer membrane. LPS released into ay b bound by a specific protein--lipopoly pr in (LBP). The LBP-LPS complex is recognized by mac use it to secrete potent cytokines (including TNF-(A kin). In addition, LPS can stimulate lymphocytes to pr amm (IFN-(Gamma)), which intensifies the macrophage ou) nd interleukin-1. The amount of the mediators produce umably depends on the intensity of the stimulus. It me manifestations, the output of TNF-(Alpha) and i at that it produces an overwhelming induction of iNOS al and smooth-muscle cells; this would result in p ived, severe vasodilatation.

Gram - po teri products, including superantigens, o org isms may induce the massive activation of hos ch produce cytokines such as in turn, stimulate macrophages. (13,14) It has been propo uct of the **gram - positive** cell wall sam ndotoxin to produce effects similar to LPS-L ococcus aureus cell wall components peptic cid act together to release TNF-(Alpha) and k with iNOS expression. (16)

SIRS not c robes. The experimental basis for the induction of nts such as trauma or toxins is even less develop lt, however, to envision massive cytokine inductio l. A wide variety of stimuli can contribute to a y of OS induction and the resulting refractory hypote induction of SIRS are summarized in Figure 3.

(Figure 3 OI

Therapeuti a

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TABLE 2.-- ic Shock

Corticoster

Endotoxin
antibody
IL-1 and o nes
antibod
recepto ts (I
soluble
TNF-(Alpha)
antibody
receptor st
soluble
Nitric oxid e
competi itors , L-NAME)
Prostaglan ors (en)
Adhesion m agoni
Pentoxyfyl

Clinical t anti to LPS or cytokines have been equally disappointing. I ials w n antiserum to a mutant strain J5 of E. coli showed i urviva in patients with gram-negativ ctions.(22) The human biologic product, howeve a risk ansmission of infectious agents that precludes this a Monocl antibodies to endotoxin were thus developed; the m ibody E5(23) and the **humanized** murine **monoclo** were shown to be safe. Phase III trials with HA- 5(26,27 led to show a significant reduction in mortality ra gh E5 ap ly provided some protection from the development lt respi y distress syndrome. Antibodies to TNF-(Alpha) als how a si ant reduction in mortality rates in septic shock.(2 d interl -6 was a poor prognostic indicator for mortality r er, and leukin-6 levels decreased with anti-TNF-(Alpha . A natu occurring receptor antagonist for interleukin-1 (been pr d in large amounts by recombinant technology, but hase II ial showed no survival-related benefit.(29) Th atu occurring soluble decoy receptor for tumor necrosis sed i ically ill patients. In addition, in a double-blind rolled the treatment of patients in septic shock wi protein links the TNF-(Alpha) receptor to an immunoglobul of IgG1) wed increased mortality rates at the higher doses em he study. In summary, treatment with polyclonal anti ars to b e efficacious than treatment with **monoclonal** ant it it is ctical. Some of the **monoclonal** antibodies did target, they did not neutralize its activity. The a ock bett rlier in the infection. The treatment of se ytok ntibodies has reminded us of the complexity of t work ingle cytokine mediates sepsis. Treatment with **monoc** antibodies against several cytokines may ctive.

Other th ssibilit nclude th natural compound, leukocyte bacte meabilit easing protein. This compound can compete with LB ithout p ing macr age activation. The exogenously ad e bacter l-permeab ity increasing protein is hoped to bind L t can bi LBP and tivate macrophages.(31) Other antagonis flammat sponse t at have been suggested and tried include m t bloc dhesion of inflammatory cells to vascular endoth bloc kin emigr ion into tissue) and molecules that NF (Al h of t strategies currently appears to hav imit atio the int ention is undertaken after the NOS i ivated, is litt hat can be done to reverse the on ty of th ent vas lating system.

In anima sepsis, possibl administer an antagonist bef time of, en shor after administering the septic stimulu achieve ntial acy, as was observed with corticoste inherent s in the cognition of sepsis in patients often te inte ons wh psis is at a well-advanced tim t ent in tensive, at which point normal compens ul or isms be exhausted, NOS may be expressed e hi vi inica sis, although highly speculative, s e obser that interventions that are effective in p ontrolle ies usi animals are substantially less effective n counte ctive-- the clinical arena.

Consider ing ro r NO. in m ing septic
hypotension, a nis s, as argi logues (Figure 3),
valuable in se ion mar nt? Cli perience is scant.
Petros(32) des OS inhib treatme two septic patients who
were in extremi neither ent wa ed to survive, one
did; both pati to have ive pre sponses to the
arginine analo econd pl -control udy,(33) which
involved twelv , an ar e analo was again an effective
pressor but wa ly d with shed cardiac output and
continued high argini logue administered to
eight patients si e produc eased blood pressure
and cardiac ou a c vascul tance and pulmonary
vascular resis ese could ed by the
administration e.(34) relimi orts of phase I
dose-escalatin lies OS inh -methyl-L-arginine in
13 and 32 pati ic s showed ed vasopressor
requirements a e eff

Why have wi gonists disappointing thus far?
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blood flow. NO ation, y be beneficial
during hypoper re is slo d flow and a tendency
to clot. NO is m many ess physiologic
functions; com io ynthes well be expected to
have adverse e

A reason ther could be rtially inhibit NO
production--ac iz osed t gl inhibition. A global
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beneficial eff ld onl ved in a relatively
narrow dose ra e asso h increased
mortality rate ing an S-induced
hypotension an ice g deficient in NOS.
Heterozygotes of L hypotension and
also survived. ge speci inhibitor (without
complete inhib be a s ial benefit.
Alternatively, alized i of all nitric oxide
synthases in t useful ing the hypotension
of septic shoc be parti useful in
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Future d of septi may include a
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Unfortunately, been o n human cells.(38)
Finally, recen perfusi dotoxin-septic rats
with polymeriz rdiac an dysfunction in a
manner not obs or othe expanders.(39) One
explanation of o-in ser n extracellular
scavenger of N ential llular messenger
functions.

Medical ed sep drome and septic
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elucidation of logy get another example
of how insigh the of more effective
approaches to

Acknowle
This wor Al 256 the US Public
Health Service lth,

REFERENC

(1.) Mem of Ch icians/Society of
Critical Care ce Co at the American
College of Che itical dicine Consensus

0008947781 BIOSIS NO.: 199396112197
A modified enzyme-linked immunosorbent ... for measuring type-specific anti-pneumococcal capsular polysaccharide ... bodies
AUTHOR: Konradsen Helle Bossen (reprint ... en Uffe B Skov; Henrichsen Jorgen
AUTHOR ADDRESS: Dep. Bacteriol., Div. ... Microbiol., Statens Serum Institut, Artillerivej 5, 2300 ... S, Denmark**Denmark
JOURNAL: Journal of Immunological Meth ... (1): p13-20 1993
ISSN: 0022-1759
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have developed a ... y determination, superior to others hitherto described, ... coating is achieved using phenylated pneumococcal capsular pol ... es as coating antigen. The specificity of the assay is ... e inhibition by antibodies against the species-specific ... gen, C-polysaccharide (C-Ps). The method is sensitive, ... roducible, fast and easy to work with and can be used for both ... lin class and subclass antibody determinations.

DESCRIPTORS:
MAJOR CONCEPTS: Clinical Endocrinolog ... Medicine, Medical Sciences; Hematology--Human Medicin ... Medica ...; Immune System--Chemical Coordination and Homeosta ... Infe ... abolism; Pathology; Pharma ...logy
BIOSYSTEMATIC NAMES: ... Eubacteria, Bacteria, Microo ...anisms; Homi ... ...a, Vertebrata, Chordata, Animali ...; Muridae--Ro ... ...brata, Chordata, Animalia
ORGANISMS: ... **positive** Cocci); Peptostrepto ...coccus magnus (...am - ... Cocci); human (Hominidae); mouse (Muridae
COMMON TAXONOMIC TERMS: Bacteria; Eu ... Microorganisms; Humans; Primate ...; Animals; Chor ... Mamm ... Human Vertebrates; Nonhuman Mammal ... Rodents; Verte ...
MISCELLANEOUS TERMS: AFF ... ...Y CHRO ...; CHIMERIC RECOMBINANT ANTIBO ...; FAB FRAGMENT; ... AGMEN ... ENGINEERING; **HUMANIZED** ANTIBO ...; IMMUNOGLOB ... MUN ...; IMMUNOGLOBULIN M; IMMUNO ...GIC ...THOD; ... AL ... RIFICATION METHOD

0008947780 BIOSIS NO.: 199396112196
Purification of antibodies using protein L-binding framework structures in the light chain variable domain
AUTHOR: Nilson Bo H K (Reprint); Logdberg Lennart; Kastern William; Bjorck Lars; Akerstrom Bo
AUTHOR ADDRESS: Dep. Med. Physiol. Chem., Univ. Lund, P.O. Box 94, S-221 00 Lund, Sweden**Sweden
JOURNAL: Journal of Immunological Methods 164 (1): p33-40 1993
ISSN: 0022-1759
DOCUMENT TYPE: Meeting
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein L from the bacterial species Peptostreptococcus magnus binds specifically to the variable domain of Ig light chains, without interfering with the antigen-binding site. In this work a genetically engineered fragment of protein L, including four of the repeated Ig-binding repeat units, was employed for the purification of Ig from various sources. Thus, IgG, IgM, and IgA were purified from human and mouse serum in a single step using protein L-Sepharose affinity chromatography. Moreover, human and mouse monoclonal IgG, IgM, and IgA, and human IgG Fab fragments, as well as a mouse/human chimeric recombinant antibody, could be purified from cultures of hybridoma cells or antibody-producing bacterial cells, with protein L-Sepharose. This was also the case with a humanized mouse antibody, in which mouse hypervariable antigen-binding regions had been introduced into a protein L-binding kappa subtype III human IgG. These experiments demonstrate that it is possible to engineer antibodies and antibody fragments (Fab, Fv) with protein L-binding framework regions which can thus be utilized in a protein L-based purification protoc

0008245766 BIOSIS NO.: 199293088657

SPECIFICITY AND PROTECTIVE ACTIVITY OF MURINE MONOCLONAL ANTIBODIES DIRECTED AGAINST THE CAPSULAR POLYSACCHARIDE OF TYPE III GROUP B STREPTOCOCCI

AUTHOR: TETI G (Reprint); CALAPAI M; CALOGERO G; TOMASELLO F; MANCUSO G; GALLI A; RIGGIO G

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JOURNAL: Hybridoma 11 (1): p13-22 1992

ISSN: 0272-457X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: We have obtained 41 **monoclonal** antibodies directed against type III group B streptococci by immunizing Balb/c mice with formalin-killed bacteria. All of these antibodies reacted with purified type-specific carbohydrate by enzyme-linked immunosorbent assay and immunoprecipitation tests. The epitope recognized by all of these antibodies was associated with terminal sialic acid residues, as indicated by abrogation of immune reactions by treatment of the type-specific carbohydrate with neuraminidase. Two purified **monoclonal** antibodies (the IgM P9D8 and the IgG3 P4F12) were further characterized for their protective activity in a neonatal rate model of infection. P9D8 and P4F12 antibodies were significantly protective when administered in a dose of 0.5 and 2.5 mg/kg, respectively, at the same time as 3 .times. 105 colony forming units of type III streptococci. Protection was still observed when the antibodies were given up to 9h after challenge. No protection was afforded against infections with type Ib/c and II streptococci. Similarly, both antibodies effectively opsonized type III, but not Ia, Ib or II bacteria, in an in vitro assay. These and similar, previously described, **monoclonal** antibodies may be useful, possibly after "**humanization**" by genetic engineering for therapy of neonatal group B streptococcal infections.

DESCRIPTORS: HUMAN IMMUNE REACTION IMMUNOGLOBULIN M IMMUNOGLOBULIN G GENETIC ENGINEERING ELISA

DESCRIPTORS:

0006982293 BIOSIS NO.: 199039035682
MONOCLONAL **ANTIBODIES AGAINST** MICROORGANISMS
AUTHOR: LEHNER T (Reprint)
AUTHOR ADDRESS: DEP IMMUNOL, UNITED MED DENT SCH GUY'S AND ST THOMAS HOSP, LONDON, UK**UK
JOURNAL: Current Opinion in Immunology 1 (3): p462-466 1989
ISSN: 0952-7915
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: ENGLISH
DESCRIPTORS: REVIEW HUMAN VS. HUMANIZED RODENT ANTIBODY HUMAN IMMUNODEFICIENCY VIRUS EPITOPES PNEUMOCYSTIS-CARINII PNEUMONIA DIAGNOSIS STAPHYLOCOCCUS-AUREUS TOXIC SHOCK SYNDROME ANTI-LIPOPOLYSACCHARIDE SCHISTOSOMA-MANSONI STREPTOCOCCUS-MUTANS COLONIZATION PASSIVE IMMUNIZATION
DESCRIPTORS:
MAJOR CONCEPTS: Dental Medicine--Human Medicine, Medical Sciences; Immune System--Chemical Coordination and Homeostasis; Infection; Microbiology; Parasitology; Pharmacology; Pulmonary Medicine--Human Medicine, Medical Sciences; Serology--Allied Medical Sciences; Toxicology
BIOSYSTEMATIC NAMES: Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms; Micrococcaceae-- **Gram - Positive** Cocci, Eubacteria, Bacteria, Microorganisms; **Gram - Positive** Cocci--Eubacteria, Bacteria, Microorganisms; Sporozoa--Protozoa, Invertebrata, Animalia; Trematoda--Platyhelminthes, Helminthes, Invertebrata, Animalia; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia ; Rodentia--Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: DNA and RNA Reverse Transcribing Viruses; Viruses ; Bacteria; Eubacteria; Microorganisms; Protozoans; Helminths; Invertebrates; Platyhelminths; Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates ; Nonhuman Mammals; Rodents; Vertebrates
CONCEPT CODES:

01779194 SUPPLIER NUMBER: 20902118 (THIS IS THE FULL TEXT)
Nitric oxide and septic shock: from bench to bedside.
Kuhl, Sarah J.; Rosen, Henry
The Western Journal of Medicine, v168, n3, p176(6)
March,
1998
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0093-0415
LANGUAGE: English RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE:
Professional
WORD COUNT: 4335 LINE COUNT: 00379

AUTHOR ABSTRACT: Refractory hypotension with end-organ hypoperfusion is an ominous feature of inflammatory shock. In the past fifteen years, nitric oxide (a diffusible, short-lived product of arginine metabolism) has been found to be an important regulatory molecule in several areas of metabolism, Including vascular tone control. Vascular endothelial cells constitutively produce low levels of nitric oxide that regulate blood pressure by mediating adjacent smooth-muscle relaxation. In an inflammatory shock state, cytokines, like interleukin-1 and tumor necrosis factor-(Alpha), induce a separate, high-output form of the enzyme that synthesizes nitric oxide in both endothelial and smooth-muscle cells. The ensuing high rates of nitric oxide formation result in extensive smooth-muscle relaxation, pressor refractory vasodilation, and--ultimately--shock. The concept of the pathogenesis of inflammatory shock explains many limitations of current therapies and may foster the development of new interventions to mitigate the effects of nitric oxide overproduction in this syndrome. (Kuhl SJ, Rosen H. Nitric oxide and septic shock--from bench to bedside. West J Med 1998; 168:176-181)

TEXT:

Septic shock remains a clinical problem with high mortality rates, and therapy is mainly supportive. We review the evidence for the role of nitric oxide in mediating the hypotensive features of septic shock. Therapeutic implications are then discussed.

Case Presentation

A 72-year-old man with insulin-dependent diabetes mellitus was brought to the emergency department. He had been in his usual state of health on the evening before admission, but was confused and unable to get out of bed the following morning. On physical examination, the patient was stuporous and disoriented. His blood pressure was 95/50 mm of mercury; regular pulse, 110 beats per minute; and temperature, 38.3 (degrees) C (101 (degrees) F). Respiration was shallow at a rate of 22 per minute. His leukocyte count was 12,000, with a left shift; a urine gram stain identified many leukocytes and gram-negative rods per high power field. Despite broad spectrum antimicrobial therapy, vigorous volume resuscitation, and intravenous vasopressors, his condition continued to deteriorate: he experienced a further drop in blood pressure, the onset of adult respiratory distress syndrome, and oliguria. The patient died with cardiac arrhythmia. Blood cultures grew Escherichia coli, susceptible to all antibiotics that had been administered. Results of a postmortem examination showed multiple organ failure consistent with prolonged hypotension and sepsis. No additional predisposing factors to infection were discovered.

The Spectrum of Sepsis

The patient's initial presentation--which included fever, tachycardia, and hypotension--and his progression to pressor-refractory shock with multiple organ failure represents the continuum of the systemic inflammatory response to various agents. **Gram - positive** and noninfectious agents can produce a syndrome with characteristics indistinguishable from those of classic gram-negative sepsis; the syndrome has thus been named the systemic inflammatory response syndrome (SIRS).(1) Table 1(1) describes the progression of SIRS manifestations, from abnormal vital signs and an elevated or decreased leukocyte count or bandemia, through various degrees of end-stage organ dysfunction and pressor refractory hypotension. Our patient presented at a point late in this progression, and medical intervention was unsuccessful. A prominent feature of septic shock--severe refractory hypotension and its possible relationship with the newly recognized vasoregulatory molecule, nitric oxide (NO)--will be the focus of this review.

TABLE 1.--Definitions

Systemic inflammatory response syndrome (SIRS)

Premonitory SIRS:

Abnormal vital signs:

tachypnea, tachycardia, hyper- or hypothermia

Early SIRS:

Above plus evidence of early end organ dysfunction:

oliguria, hypoxemia, confusion, elevated lactate.

SIRS with hypotension:

Above plus hypotension responsive to fluid resuscitation

or pressor agents.

Refractory hypotension:

SIRS with hypotension unresponsive to fluid resuscitation

or pressor agents.

Sepsis and septic shock are SIRS resulting from infection.

Normal Vasoregulatory Properties of NO.

The discovery of NO, as a human regulatory molecule is relatively recent. In 1980, Furchgott and Zawadzki(2) found that the ability of acetylcholine to dilate arteries was dependent on a short-lived, low-molecular weight product of endothelial cells, designated endothelium-derived relaxation factor (Figure 1). In 1987, endothelium-derived relaxation factor was reported to be NO.(3) Until that point, the inorganic oxides of nitrogen were thought to have little or no role in normal human physiology. We now recognize that endothelial cells continuously produce low levels of NO, to maintain normal vascular tone, and we have observed agents that diminish endothelial production of NO, to cause hypertension and vasoconstriction.(4) Furthermore, pharmacologic vasodilators, such as sodium nitroprusside and nitroglycerin, are believed to exert their effects through the formation of NO.(5)

(Figure 1 ILLUSTRATION OMITTED)

NO. Chemistry and Cell Biology

NO, is unstable and has a life span of a few seconds. Because of its short half-life, the effects of NO. must occur over short distances, and biologically active NO, must be synthesized either within the cell (autocrine) or by cells nearby (paracrine). In aqueous solutions, such as plasma, NO, is oxidized mainly to nitrite,(6,7) which, in the presence of hemoglobin, is quickly oxidized to nitrate. Some of the physiologic characteristics of NO, are related to its ability to bind to heme. The binding of NO, to heme in hemoglobin results in the accelerated degradation of NO, to nitrate, a feature that may further limit the lifespan of NO, in the bloodstream. The binding of NO, to the heme of guanylate cyclase, a smooth-muscle enzyme, accelerates the conversion of guanosine triphosphate to cyclic guanosine monophosphate. The resulting increased levels of cyclic guanosine monophosphate apparently mediate muscle cell relaxation in a manner that is not well characterized.(5)

Physiologic NO, is synthesized from arginine by an enzyme complex called NO. synthase or NOS (Figure 2). Three distinct NOS enzyme complexes have been described. Neuronal nitric oxide synthase (nNOS) is found in cells of the central nervous system cells and is thought to support a neurotransmitter function. A second--constitutive NOS (cNOS)--is in endothelial cells and is thought to play a role in the maintenance of normal vascular tone. The third is a high output, inducible enzyme called inducible NOS (iNOS); this complex is found in many cell types but particularly endothelial and vascular smooth-muscle cells. It is proposed that iNOS is the enzyme that plays a major role in septic hypotension.

(Figure 2 ILLUSTRATION OMITTED)

Increased NO. Synthesis In Inflammatory States

Several observations indicate that nitrate production increases in humans in inflammatory states. In a study of normal nitrate excretion in humans,(8) one study subject serendipitously acquired infectious diarrhea and simultaneously exhibited increased nitrate excretion.(9) A second study(10) evaluated nitrate biosynthesis in renal cell carcinoma and melanoma patients who were receiving high-dose interleukin-2 therapy, which frequently produces a febrile, hypotensive state similar to septic shock. Nitrate excretion increased dramatically in these patients; the nitrate was derived from the same nitrogens of arginine that would be acted upon by the NOS enzyme complex. Another study(11) showed that in patients with septic shock, plasma nitrite and nitrate concentrations are increased and correlate directly with endotoxin concentration and cardiac output. The

same concentrations correlate inversely with systemic blood pressure, consistent with the role of NO. as a mediator of the hemodynamic disturbances in sepsis.

Inducible NO. Synthase

Cytokines that are prominent in mediating the sepsis syndrome, such as tumor necrosis factor (TNF-(Alpha)) and interleukin-1 (IL-1), induce the production of iNOS. Endothelial cells constitutively generate low levels of NO from cNOS, but they will respond to cytokines with iNOS synthesis and increased NO production. Vascular smooth-muscle cells ordinarily lack NOS activity; however, they can be induced by TNF-(Alpha) and interleukin-1 to form large amounts of iNOS. A major distinction between iNOS and cNOS is the amount of NO that is produced. The production of NO. from iNOS may be as much as 1000-fold greater than the usual levels that result from cNOS. The enzyme requires hours to appear, however, because iNOS induction requires new protein synthesis. Once induced, the iNOS enzyme is likely to persist for many hours to days. The high levels of NO formed by this enzyme result in smooth-muscle cell relaxation (vasodilatation) refractory to commonly used pressor agents.(12) These features make iNOS induction an appealing prospect for mediating the pressor refractory hypotension that appears several hours into the development of the sepsis syndrome.

A Set of Models for Septic Hypotension

Gram-negative sepsis. Grain-negative bacteria such as E. coli have an endotoxin or lipopolysaccharide (LPS) component to their outer membrane. LPS released into the circulation may be bound by a specific protein--lipopolysaccharide binding protein (LBP). The LBP-LPS complex is recognized by macrophages, which causes it to secrete potent cytokines (including TNF-(Alpha) and interleukin-1). In addition, LPS can stimulate lymphocytes to produce interferon gamma (IFN-(Gamma)), which intensifies the macrophage output of TNF-(Alpha) and interleukin-1. The amount of the mediators produced by the macrophage presumably depends on the intensity of the stimulus. It is possible that, in extreme manifestations, the output of TNF-(Alpha) and interleukin-1 is so great that it produces an overwhelming induction of iNOS in vascular endothelial and smooth-muscle cells; this would result in pressorrefractory, long-lived, severe vasodilatation.

Gram - positive sepsis. Bacterial products, including superantigens, of **gram - positive** organisms may induce the massive activation of host lymphocytes, which then produce cytokines such as interleukin-2 and IFN-(Gamma) that, in turn, stimulate macrophages.(13,14) It has been proposed that some products of the **gram - positive** cell wall interact with LBP in the same manner as endotoxin to produce effects similar to LPS-LBP.(15) In animals, Staphylococcus aureus cell wall components peptidoglycan and lipoteichoic acid act together to release TNF-(Alpha) and IFN-(Gamma) and cause shock with iNOS expression.(16)

SIRS not clearly associated with microbes. The experimental basis for the induction of SIRS by noninfectious agents such as trauma or toxins is even less developed.(17) It is not difficult, however, to envision massive cytokine induction via these agents as well. A wide variety of stimuli can contribute to a final common pathway of iNOS induction and the resulting refractory hypotension. The models for the induction of SIRS are summarized in Figure 3.

(Figure 3 ILLUSTRATION OMITTED)

Therapeutic Considerations

Although much work is needed to confirm and extend these pathophysiologic concepts, the above evidence suggests new approaches to the treatment and prevention of sepsis. Newly developed pharmaceutical and biotechnology agents have led to a variety of options (Table 2). Those with the most extensive history are glucocorticoids, which recently have been shown to increase the cellular content of a cytosolic protein I(Kappa)B (1-kappaB)(18,19) that inhibits the induction of inflammatory cytokines in resting macrophages. Corticosteroids can thus prevent cytokine activation of macrophages; however, it is expected that they would have little effect if given after macrophage activation--which is the circumstance that occurs in clinically detectable sepsis. In studies involving sepsis in animals, glucocorticoids have long been recognized as effective, especially when given before a bacterial or lipopolysaccharide (LPS) challenge. (No overall benefit has been demonstrated in human trials.(20)) Prostaglandin inhibitors such as ibuprofen improve survival in animals when given before the onset of sepsis. In a human trial, ibuprofen did not prevent the development of shock or acute respiratory distress syndrome, and it did not

improve survival.(21)

TABLE 2.--Therapy for Refractory Septic Shock

Corticosteroids

Endotoxin

- antibody

IL-1 and other cytokines

- antibody
- receptor antagonists (IL-1ra)
- soluble receptor

TNF-(Alpha)

- antibody
- receptor antagonist
- soluble receptor

Nitric oxide synthase

- competitive inhibitors (L-NMMA, L-NAME)

Prostaglandin inhibitors (Ibuprofen)

Adhesion molecule antagonists

Pentoxyfylline

Clinical trials with antibodies to LPS or cytokines have been equally disappointing. Initial trials with human antiserum to a mutant strain J5 of E. coli showed improved survival rates in patients with gram-negative bacteremia or focal gram-negative infections.(22) The human biologic product, however, carries a risk of transmission of infectious agents that precludes this approach. **Monoclonal** antibodies to endotoxin were thus developed; the murine **monoclonal** antibody E5(23) and the **humanized** murine **monoclonal** antibody HA-1A(24) were shown to be safe. Phase III trials with HA-1A(25) and E5(26,27) failed to show a significant reduction in mortality rates, although E5 apparently provided some protection from the development of the adult respiratory distress syndrome. Antibodies to TNF-(Alpha) also did not show a significant reduction in mortality rates in septic shock.(28) Increased interleukin-6 was a poor prognostic indicator for mortality rates, however, and interleukin-6 levels decreased with anti-TNF-(Alpha) treatment. A naturally occurring receptor antagonist for interleukin-1 (IL-1ra) has been produced in large amounts by recombinant technology, but, again, a phase III trial showed no survival-related benefit.(29) The levels of a naturally occurring soluble decoy receptor for tumor necrosis factor increased in critically ill patients. In addition, in a double-blind placebo-controlled trial, the treatment of patients in septic shock with a fusion protein that links the TNF-(Alpha) receptor to an immunoglobulin base (Fc of IgG1) showed increased mortality rates at the higher doses employed in the study.(30) In summary, treatment with polyclonal antibodies appears to be more efficacious than treatment with **monoclonal** antibodies, but it is impractical. Some of the **monoclonal** antibodies did bind to the target, but they did not neutralize its activity. The antibodies work better earlier in the infection. The treatment of sepsis with anticytokine antibodies has reminded us of the complexity of the cytokine network: no single cytokine mediates sepsis. Treatment with a mixture of **monoclonal** antibodies against several cytokines may be more effective.

Other therapeutic possibilities include the natural compound, leukocyte bactericidal-permeability increasing protein. This compound can compete with LBP for LPS without producing macrophage activation. The exogenously added leukocyte bactericidal-permeability increasing protein is hoped to bind LPS before it can bind to LBP and activate macrophages.(31) Other antagonists of the inflammatory response that have been suggested and tried include molecules that block the adhesion of inflammatory cells to vascular endothelium (thus blocking their emigration into tissue) and molecules that antagonize TNF-(Alpha) Each of these strategies currently appears to have a common limitation: if the intervention is undertaken after the NOS has been activated, there is little that can be done to reverse the ongoing activity of this potent vasodilating system.

In animal models of sepsis, it is possible to administer an antagonist before, at the time of, or even shortly after administering the septic stimulus and still achieve substantial efficacy, as was observed with corticosteroids. The inherent delays in the recognition of sepsis in patients often result in late interventions when sepsis is at a well-advanced stage. By the time the patient is hypotensive, at which point normal compensatory vasoregulatory mechanisms would be exhausted, NOS may be expressed extensively. This view of clinical sepsis, although highly

speculative, strengthens the observation that many interventions that are effective in preliminary controlled studies using animals are substantially less effective--or are even counterproductive--in the clinical arena.

Considering the emerging role for NO. in mediating septic hypotension, are NOS antagonists, such as arginine analogues (Figure 3), valuable in septic hypotension management? Clinical experience is scant. Petros(32) described the NOS inhibitor treatment of two septic patients who were in extremis. Although neither patient was expected to survive, one did; both patients seemed to have positive pressor responses to the arginine analogues. In a second placebo-controlled study,(33) which involved twelve individuals, an arginine analogue was again an effective pressor but was unfortunately associated with diminished cardiac output and continued high mortality rates. Another arginine analogue administered to eight patients with the sepsis syndrome produced increased blood pressure and cardiac output, as well as systemic vascular resistance and pulmonary vascular resistance.(34) These changes could be reversed by the administration of L-arginine.(34) Two preliminary reports of phase I dose-escalating safety studies of the NOS inhibitor N-methyl-L-arginine in 13 and 32 patients in septic shack(35) showed decreased vasopressor requirements and no adverse effects.

Why have the results with NO antagonists been disappointing thus far? NO is an important mediator of neurotransmission. It is also used to maintain the splanchnic circulation, and it functions to regulate pulmonary blood flow. NO inhibits platelet aggregation, which may be beneficial during hypoperfusion, at which time there is slow blood flow and a tendency to clot. NO is an important mediator of many essential physiologic functions; complete inhibition of NO. syntheses might well be expected to have adverse effects.

A reasonable goal of therapy thus could be to partially inhibit NO production--achieving localized, as opposed to global, inhibition. A global inhibition of all NOS enzyme complexes would have to be administered with extreme care. In one trial using animals to study endotoxic shock, a beneficial effect of NO antagonists could only be observed in a relatively narrow dose range, and higher doses were associated with increased mortality rates.(10) In another study using animals, LPS-induced hypotension and death were observed in mice genetically deficient in NOS. Heterozygotes had an intermediate amount of LPS-induced hypotension and also survived.(36) This suggested that a specific NOS inhibitor (without complete inhibition of the enzyme) might be a substantial benefit. Alternatively, the development of a localized inhibitor of all nitric oxide synthases in the vascular bed could be useful in treating the hypotension of septic shock .37 NO antagonists may be particularly useful in vasopressor refractory shock because of the paucity of other effective treatment.

Future directions for the therapy of septic shock may include a search for more specific inhibitors of NOS that allow continued function of the constitutive endothelial and neural NO synthases. Another possibility is to search for guanylate cyclase inhibitors or antagonists of cyclic guanosine monophosphate. Yet another approach might involve identifying physiologic down-regulators of NOS. In a murine system, the cytokines interletikin-4 and interleukin-10 have been shown to down-regulate NOS. Unfortunately, similar effects have not been observed in human cells.(38) Finally, recent work has indicated that perfusion of endotoxin-septic rats with polymerized hemoglobin reverses cardiac and renal dysfunction in a manner not observed with NOS inhibitors or other volume expanders.(39) One explanation offered was that the hemoglobin served as an extracellular scavenger of NO without affecting its essential intracellular messenger functions.

Medical management of fully developed sepsis syndrome and septic shock continues to be a formidable clinical problem. The search for useful interventions has been put on a more rational footing by advances in the basic knowledge of cytokine and NO.-mediated vasoregulation. The elucidation of vasoregulatory cell physiology provides yet another example of how insights from the "bench" support the development of more effective approaches to therapy at the bedside.

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RELATED ARTICLE: ABBREVIATIONS USED IN TEXT

LBP = LPS binding protein SIRS = systemic inflammatory response syndrome NO. = nitric oxide NOS = NO synthase EL = interleukin TNF-(Alpha) = tumor necrosis factor LPS = lipopolysaccharide IFN-(Gamma) = interferon

gamma

SPECIAL FEATURES: table; chart; illustration
DESCRIPTORS: Nitric oxide--Physiological aspects; Septic shock--
Physiological aspects
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